THE
BRITISH JOURNAL OF SURGERY

VOL. XXXVIII OCTOBER, 1950 No. 150

PHARYNGEAL DIVERTICULA*

OBSERVATIONS ON THEIR EVOLUTION AND TREATMENT

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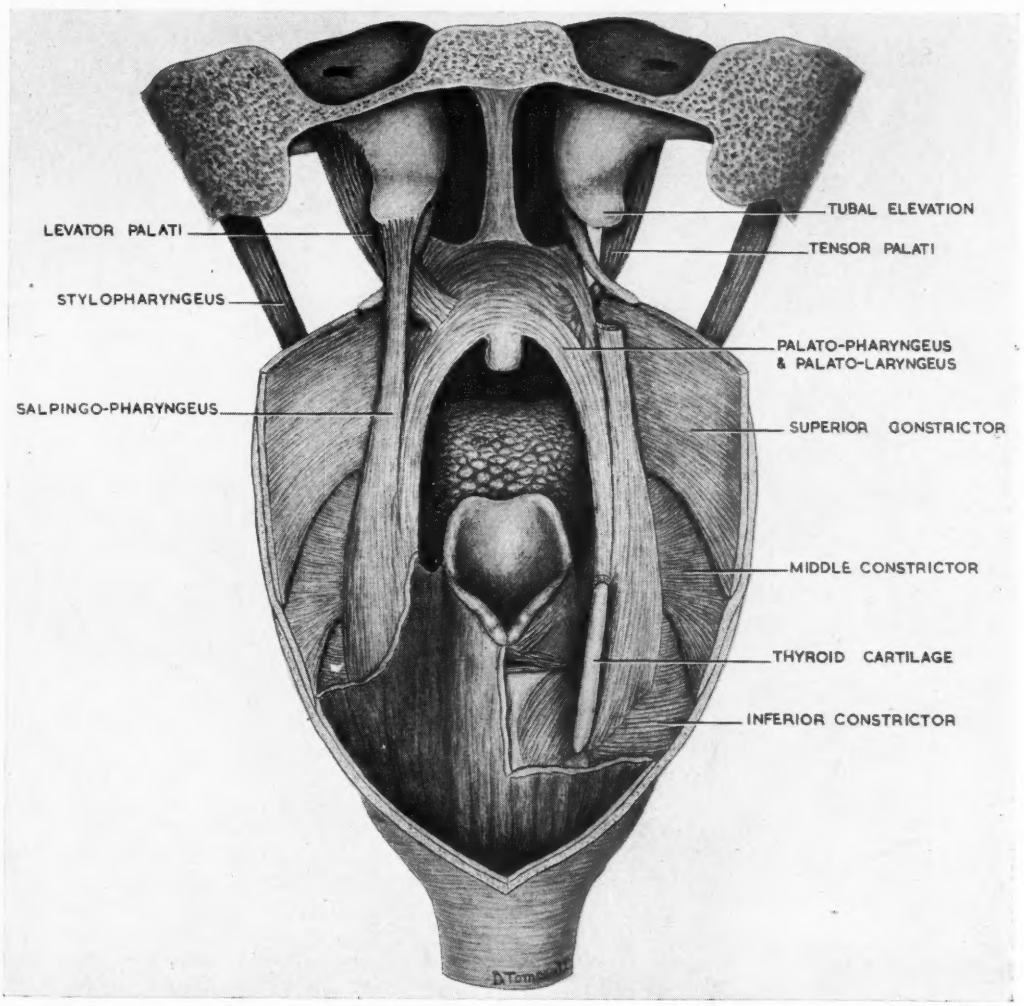


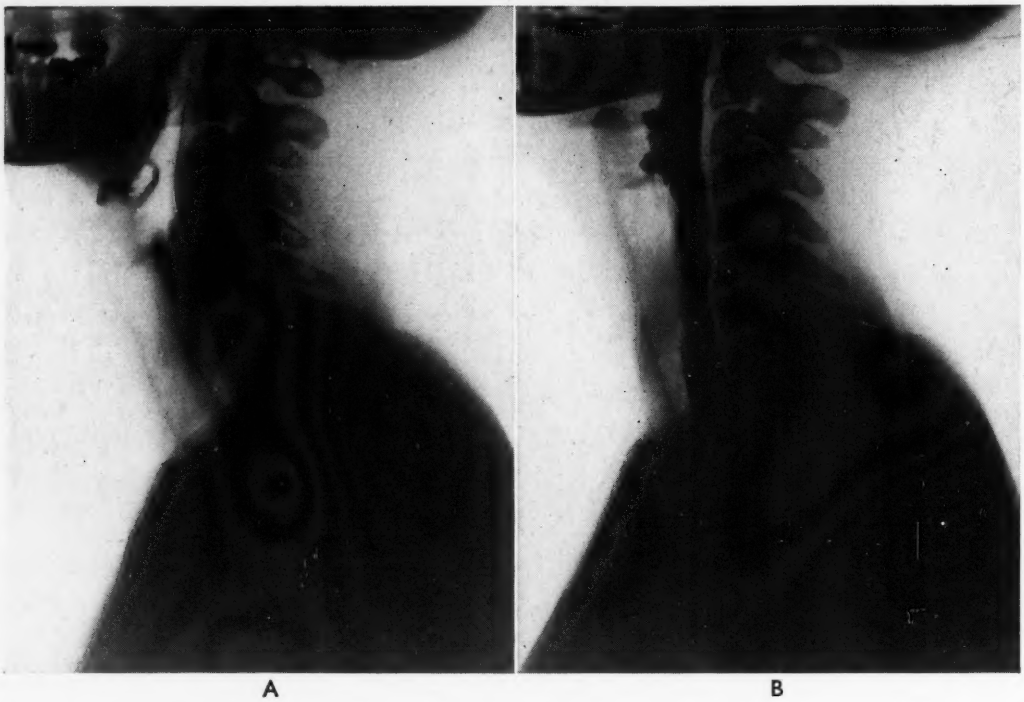
FIG. 179.—Human pharynx open from behind, to show the elevator and constrictor muscles. (*Modified from "Gray's Anatomy"*, 19th ed., 1916.) (*From "Comparative Anatomy and Physiology of the Larynx"*, Negus, V. E., 1949. *London: Heinemann.*)

THE subject of diverticula of the pharynx is one that has interested many; that this communication should be given by a laryngologist is due to the opportunities afforded to a specialist in this region of studying, by direct observation, the mechanism of swallowing, and of elucidating the reasons for herniation of the posterior wall of the hypopharynx.

My primary object in making this communication lies in the assumption that a pharyngeal diverticulum in its early stages is the result, and not the cause, of

*A Lecture delivered under the auspices of the Institute of Laryngology and Otology and the Royal College of Surgeons of England.

dysphagia. One has seen cases where the operation for removal of a pouch has been successfully carried out, but, regrettably, with no relief of difficulty in swallowing. It is essential that the basic principles should be clear to anyone who embarks on the treatment of a case, and that is my main reason for offering this contribution. I propose, with this end in view, to discuss the mechanism of the second stage of swallowing, and, after elucidating the reason for the appearance of a pouch, to put forward some observations on the rationale of treatment.



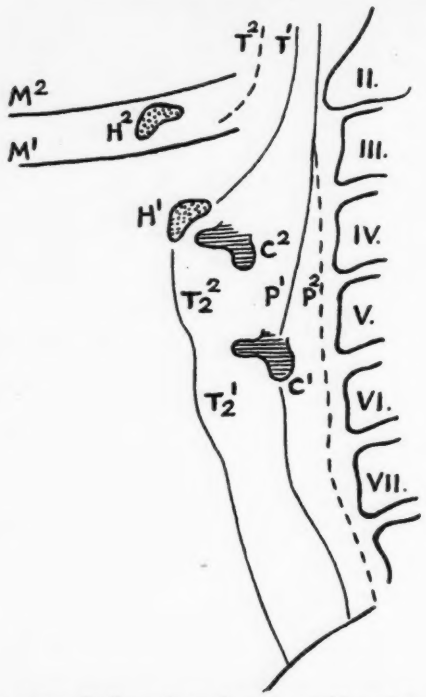


FIG. 180.—Radiograph to show the position of the adult human larynx (A) at rest, and (B) during deglutition. The rise of the larynx is well seen. The key shows the position during respiration (1) and deglutition (2) of M, Mandible; T_2, Tongue; H, Hyoid bone; C, Cricoid; T_2, Thyroid cartilage; P, Pharynx. (*Radiographs kindly lent by Dr. T. V. Crichlow.*)

The operation itself, at the present time, is one without undue risk, and the technique offers no great difficulty to one conversant with the surgery of the neck, whether he be general surgeon or laryngologist.

EVOLUTIONARY FACTORS

Twenty-five years ago I presented a communication on this subject, and I propose to repeat many of the previous observations.

Second Stage of Swallowing.—Animals with no pulmonary apparatus have a simpler mechanism of swallowing than those which possess lungs; a tube surrounded by longitudinal and circular muscle executes peristaltic waves which propel food into the stomach. There is not the same division into stages as in lung-breathing species.

Lung-breathing mammals also have a muscular pharynx, the longitudinal fibres in man being represented by the palato-pharyngeus and palato-laryngeus, the stylo- and salpingo-pharyngeus, and in part the tensor and levator palati (*Fig.* 179). The first group has the function of elevating the whole pharynx at the beginning of the second stage of swallowing. The larynx rises with the pharynx, of which it forms a part of the anterior wall; it has its own muscles, the thyrohyoid in particular, to assist in its upward movement towards the hyoid bone. The hyoid itself is drawn up towards the mandible, with the thyroid cartilage closely applied to its postero-inferior surface (*Fig.* 180). The whole pharynx is, as it were, pulled up over the bolus,

which cannot retreat owing to the action of the tongue and fauces, together with the nasopharyngeal sphincter. In man the larynx is large in relation to the size of the pharynx, as it is in many mammals. This factor complicates the second stage of swallowing very considerably in comparison with some lower species, such as a chameleon (*Fig.* 181).

After initial raising of the pharynx and larynx a peristaltic wave is executed by the pharyngeal constrictors and travels downwards; it commences in the nasopharynx and terminates at the mouth of the œsophagus. We are concerned at present with the events of the second stage only, and not with the mechanism in the œsophagus.

The circular muscle-fibres in the walls of the pharynx are provided by the constrictors, of which the inferior component is of particular interest in the present inquiry.

All the evidence at my disposal assures me that any large bolus is carried through the pharynx by a force-pump action and not merely by the pull of reduced pressure, as suggested by Barclay (1930, a, b, c); anyone who has had the management of a patient with a pharyngostome will have derived visual evidence of the powerful muscular wave, which may be confirmed by actual measurement.

Alterations in Disposition of Pharyngeal Constrictors.—In most animals the fibres of the constrictors are arranged in a circular manner; in man they are oblique (*Fig.* 182). The reason for this change is descent of the larynx in the neck, with elongation of the pharynx. The larynx descends for various reasons. The first is a change in the vertebro-occipital and pituitary angles, imposed by the assumption of the erect posture; in the higher apes the attitude is slouching, and the inclination of the head is not so marked as in man, who walks erect. In primates the larynx is higher and the pharynx considerably smaller than in man (*Fig.* 183). A more important factor is recession of the jaws,

FIG. 181.—Dissection of a chameleon, exposing the diminutive larynx in the floor of a wide pharynx. An air sac lies below the commencement of a long and narrow trachea, which leads to sac-like lungs. (*From "Journal of Laryngology and Otology"*, 1931, January.)

which change their prognathous character to a position below the cranium in modern European man. The tongue remains large, but instead of lying flat in the mouth, it assumes a recurved shape, part lying in the pharynx. The larynx, closely applied

The high position occupied in most mamm ls is of advantage in respect of olfaction ; the majori / are macrosmatic, and retention of a keen sense of mell is important to the hunting carnivore and h nted herbivore. To maintain efficiency of olfa tion,

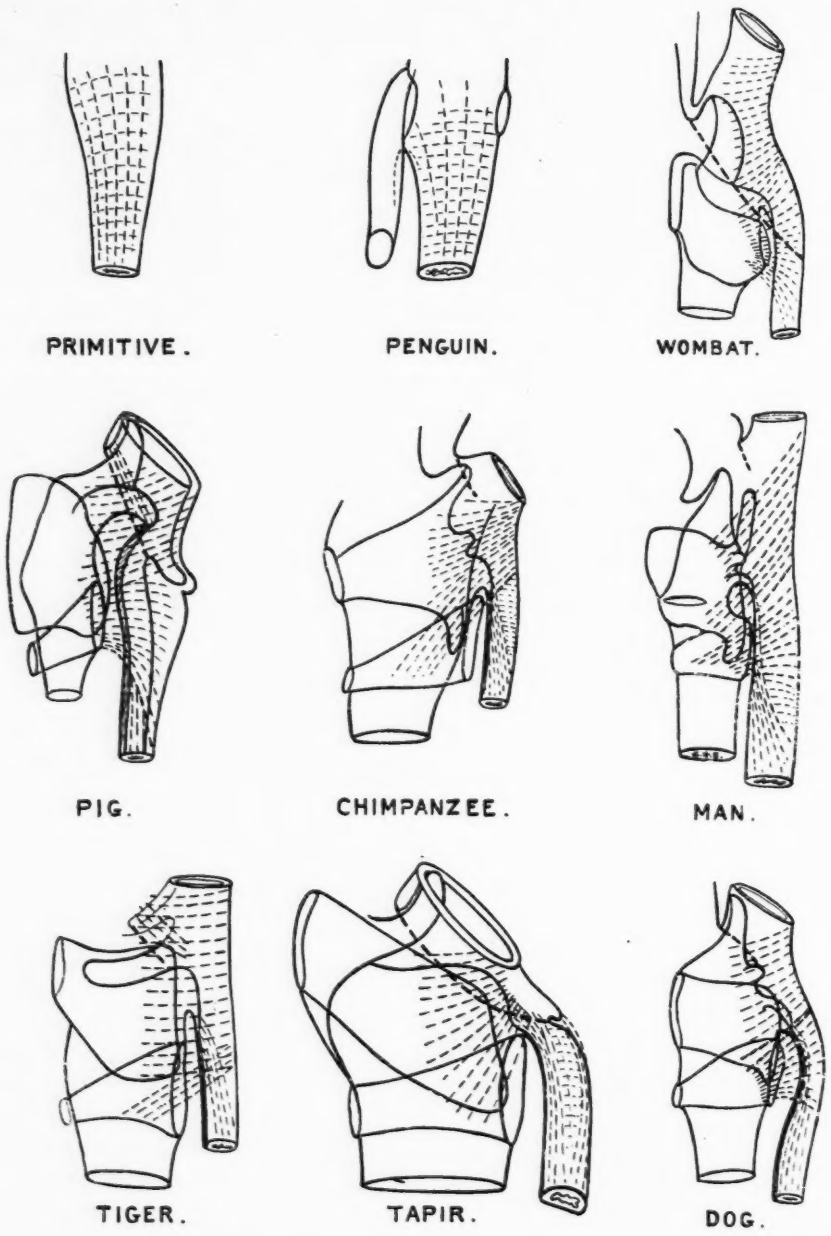


FIG. 182.—Arrangement of *inferior constrictor muscles* in various animals. The larynx is on the left and the pharynx and œsophagus on the right. In each case the dissection is viewed from the left. The epiglottis, thyroid, and cricoid cartilages, and the corniculate process of Santorini, are indicated by continuous lines. The posterior palatine fold, or arcus palatopharyngeus in the wombat (*Phascolomis mitchelli*), tapir (*Tapirus indicus*), and pig (*Sus scrofa*), is shown by a heavy interrupted line. The inferior constrictor muscles and longitudinal and circular fibres of the œsophagus are indicated by fine interrupted lines. The nasopharynx has been divided and its cut edge is shown by double circular lines. The pig has a small diverticulum above the arcus palatopharyngeus. (*From "Journal of Laryngology and Otology"*, 1925, November.)

to the hyoid system, necessarily shifts with the tongue, until it takes up a very low position in the neck. The cricoid cartilage lies opposite the sixth cervical vertebra, unlike that of lower animals, in which it is placed opposite the base of the skull.

mouth breathing must be prevented, to ensure passage of all inspired air through the nose. This is attained by approximation of the larynx to the naso-pharynx, the gap being closed anteriorly by a large epiglottis (*Fig.* 184).

In man, whose sense of smell is feeble, and in whom reliance is placed on vision, this approximation is not essential, and descent of the larynx, with a resultant gap between soft palate and epiglottis, is of little disadvantage (*Fig.* 185).

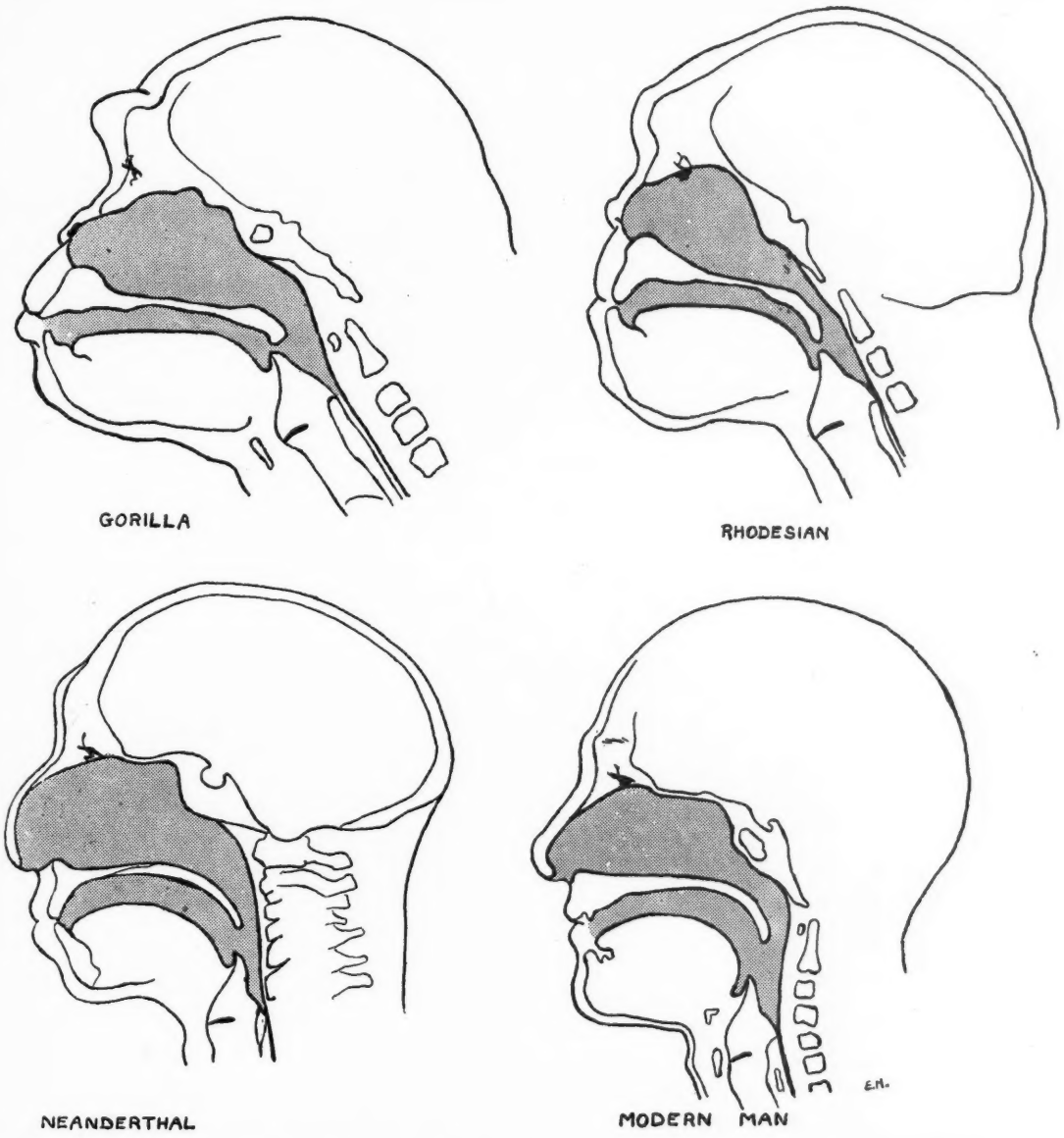


FIG. 183.—Stages in the evolution of man. Diagrammatic representation of the position of the larynx and the position and size of the pharyngeal, oral, and nasal resonators in the gorilla and in early and modern man. The diagram of the Rhodesian man is constructed from illustrations in Sir Arthur Keith's book, *The Antiquity of Man*, 1915 (London : Williams & Norgate). The author's permission was obtained. There was marked prognathism, almost to the degree seen in the gorilla. The palate was long and the tongue flat. The larynx lay high in relation to the vertebral column, although at a slightly lower level than in the ape. The epiglottis was distinctly separated from the soft palate. The larynx was probably large and funnel-shaped, as in the higher apes. The diagram of the Neanderthal woman was kindly made for me by Sir Arthur Keith ; it is a composite figure made up from a vault from Gibraltar and a mandible and spine from Palestine. The jaws have receded somewhat, and the tongue, in its backward progress, has become slightly curved. The larynx thus lies at a lower level in relation to the base of the skull and the vertebral column than in the apes. There is, however, no large pharyngeal resonator, as in modern man, in whom the jaws have still further receded but the tongue is large ; the larynx is thus forced to lie low in the neck. In this way a capacious pharynx comes into existence. The palate of Neanderthal man was slightly larger than that of modern man. The gap between the palate and the epiglottis has increased during evolutionary changes to that of modern man. (*From "Archives of Otolaryngology"*, 1938, **28**.)

Alterations in the disposition of the pharyngeal constrictors follow the change in position of the larynx. The inferior constrictor arises from the thyroid and cricoid cartilage, and in man its fibres assume an oblique direction to reach the median raphe ; the component parts of the middle and superior constrictors also have an oblique direction owing to the continuity of this tubular group of muscles (*see Fig.* 182). There is no possibility of downward displacement of the constrictors, since the median raphe is attached at its upper end to

the occiput. As the whole pharynx is free to move upwards under the influence of the elevators, the constrictors will have a less oblique inclination during the early phase of the second stage of swallowing than when at rest; but if there be any hindrance to the movement of the cricoid, the obliquity will be maintained.

During respiration the laryngeal apertu e an glottis are open, while the mouth of the œso hagu is closed (*see Fig.* 197 A). Were this not so, ai woul be drawn, by the expansion of the thoracic c ge an descent of the diaphragm, into the œsoph gus a well as into the lungs; since the œsophageal oper ing, when relaxed, is wider than the glottis, mor

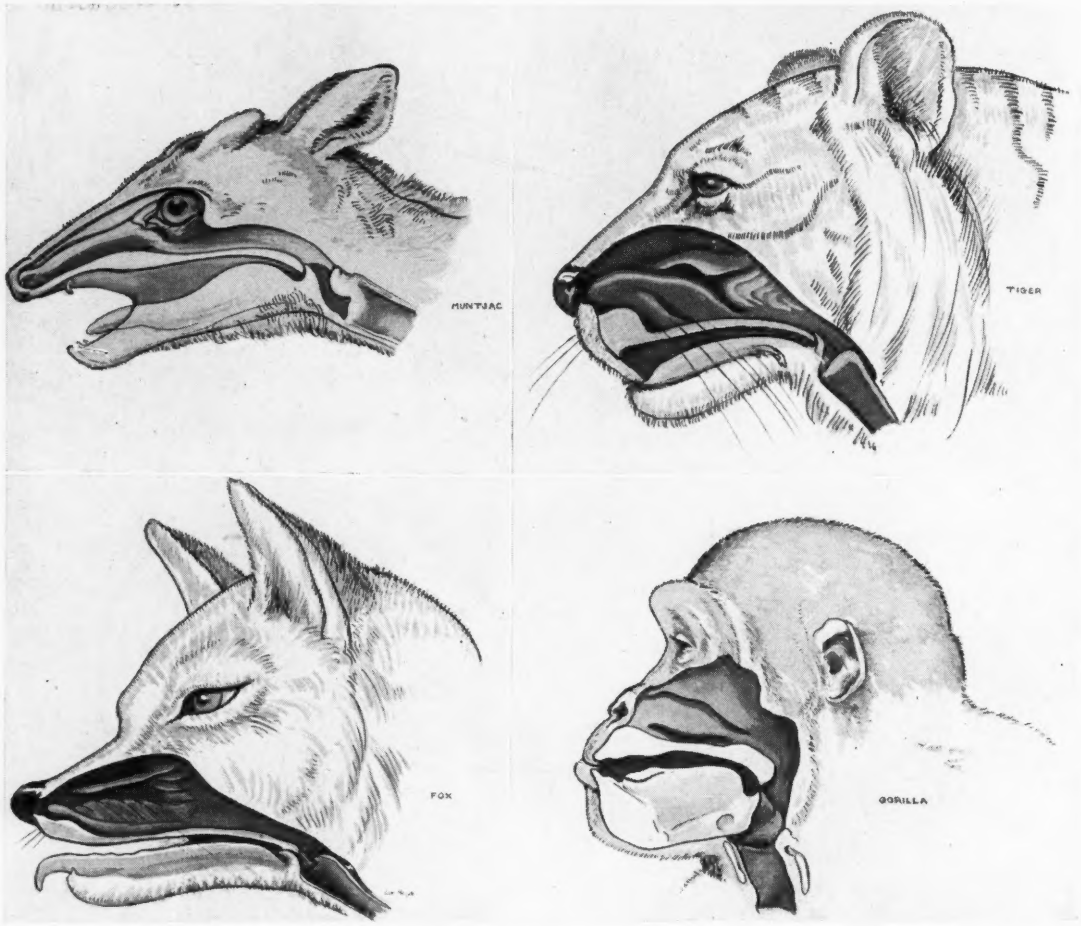


FIG. 184.—Relationship of the palate and the larynx. In keen-scented deer (*Muntjac*) the epiglottis lies above the soft palate and causes all the air to enter and leave through the nose during respiration. In carnivora (*tiger*) the same arrangement holds good to preserve the olfactory sense for the purpose of tracking prey. In wolves and the dog tribe (*fox*) (*Canis vulpes*) the epiglottis lies in contact with, but below, the palate. During inspiration air must enter by the nose and thus supply scent to the olfactory organ; the expiratory current can, on the other hand, escape through the mouth, as the epiglottis is blown down. In this way moisture is carried off the tongue to cool the animal; this mechanism is of value, because sweating is impossible. The *gorilla* relies on sight and not on scent, and no longer needs to direct air through the nose; there is, in consequence, a gap between the soft palate and epiglottis. (*Adapted from* "*Archives of Otolaryngology*", 1938, **28**.)

Reasons for the Presence of a Sphincter at the Mouth of the Œsophagus.—If the pharyngeal tube were directly continuous with the œsophagus, and if a bolus travelled down without interruption, there would be no reason for the creation of a pharyngeal diverticulum. But such is not the case, since the two sections are separated by the cricopharyngeal sphincter; the second stage of swallowing terminates and the third commences at this level.

In 1925 I advanced a reason for the presence of this powerful sphincter, which I believe offers the correct explanation.

air would enter the gullet than the lungs (*see Fig.* 197 B).

This is readily observed when an œsophagoscope is passed in a conscious patient, who becomes alarmed by a sensation of asphyxiation until the mouth of the œsophagoscope is temporarily closed to divert inspired air into the trachea.

The function of the cricopharyngeal sphincter, therefore, by remaining in contraction except when a bolus of food is passing, is prevention of œsophageal respiration; it is a function of considerable importance in all mammals, but particularly in those of arboreal habit or with an arboreal ancestry, and in

those making independent use of the forelimbs for such purposes as grasping or hugging.

Influence of Independent Forelimb Efforts.—As described elsewhere, there is assistance given, particularly in arboreal species, towards fixation of the ribs by closure of the valvular glottis during forelimb efforts (*Fig* 186). The pectoral muscles

muscular sphincter at the mouth of the œsophagus; this provides a factor in the production of herniation (*Fig.* 189).

The Cricopharyngeal Sphincter during Swallowing.—The layers constituting the walls of the pharynx are, internally, the mucous membrane, next to this the pharyngeal aponeurosis, then the

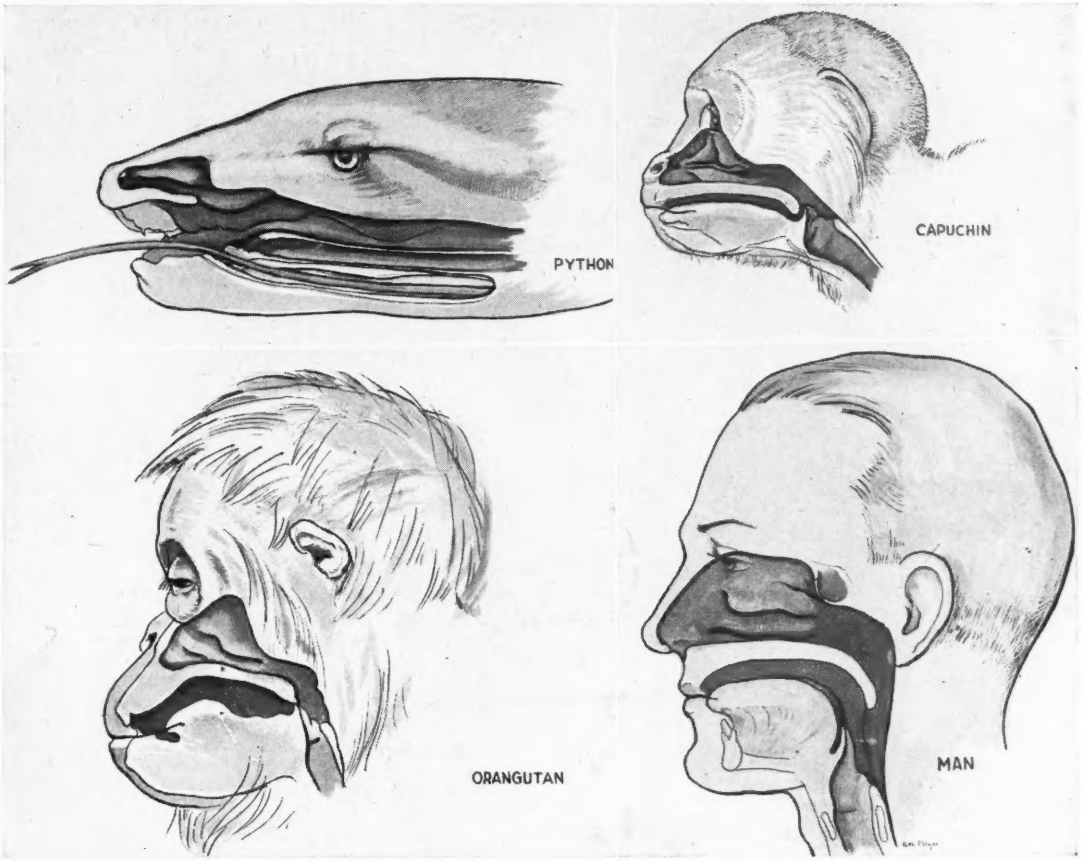


FIG. 185.—Comparative anatomy of the pharynx. Semi-diagrammatic representation of the nose, palate, tongue, pharynx, and larynx in a snake, a monkey, an ape, and a man. The elongation of the palate is well illustrated; it comes into close contact in the monkey, but in the higher apes and in man there is a gap of varying size. The larynx of the python, as in other snakes, can be protruded during the swallowing of a large bolus. (*Previously produced in "Archives of Otolaryngology"*, 1938, 28.)

need a fixed origin in order to exert the maximum pull on the forelimbs, as when climbing; if the glottis be closed at the commencement of an inspiratory effort, the prevention of entrance of air into the lungs tends to prevent expansion of the thoracic cage (*Fig.* 187). During such an effort, with reduced pressure in the thorax, there must be considerable tendency for air to be sucked into the œsophagus; a very powerful cricopharyngeal sphincter is therefore required. In most animals which use their forelimbs merely for locomotion, the larynx is not of a mechanical valvular type. In such species the possible reduction of intrathoracic pressure is of a lesser degree than in climbing animals (*Fig.* 188). The reindeer, for example, cannot close its glottis completely.

Man, who is of arboreal descent, and who makes great use of the forelimbs for grasping and other purposes, is provided with a powerfully contracting

longitudinal muscles and circular muscles, covered externally by the buccopharyngeal fascia. The latter is firmly applied to the prevertebral fascia, being held there by atmospheric pressure; the pharynx is, however, capable of sliding upwards and downwards.

The cricopharyngeal sphincter, constituting part of the circular muscle layer, is itself as firmly applied to the prevertebral fascia, and thus to the vertebral column, as if attached by ligaments. (*Figs.* 180, 197 A). The sphincter, when contracted, exerts a pull on its site of origin from the cricoid cartilage, and thus holds back the larynx with considerable force during the resting phase. But at the beginning of the second stage of swallowing, a sensory stimulus, originating in the upper posterior pharyngeal wall, is transmitted to the cricopharyngeal sphincter and leads to its inhibition and relaxation at the moment when a peristaltic wave descends

from the nasopharynx to the hypopharynx. The result is that a bolus of food, propelled by the pharyngeal force-pump, arrives at the mouth of the œsophagus at a time when the sphincter is relaxed,

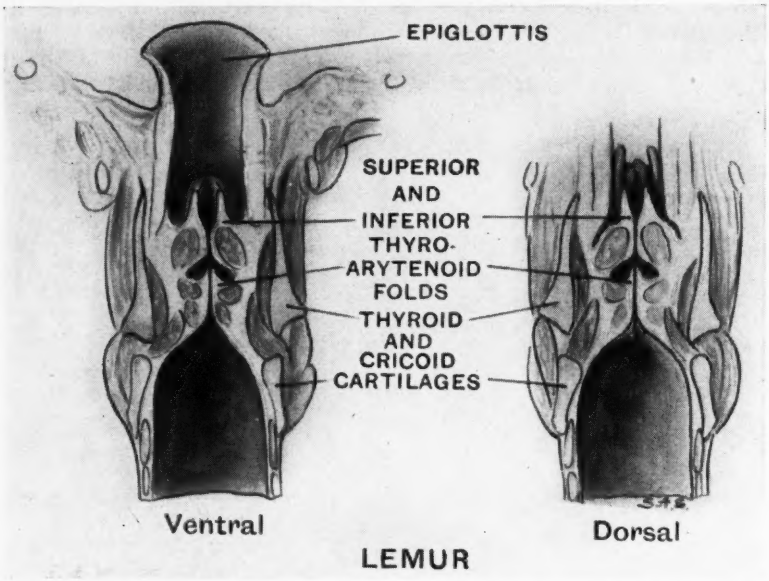


FIG. 186.—Coronal sections of larynx of *Lemur flavifrons*, to show the double inlet valve made up of the superior and inferior divisions of the thyro-arytenoid fold, with the ventricle between them. (*From "Journal of Laryngology and Otology"*, 1924, January.)

thus allowing passage of the bolus into the œsophagus.

When the sphincter relaxes the larynx is released; it first tilts forward and then moves in an oblique

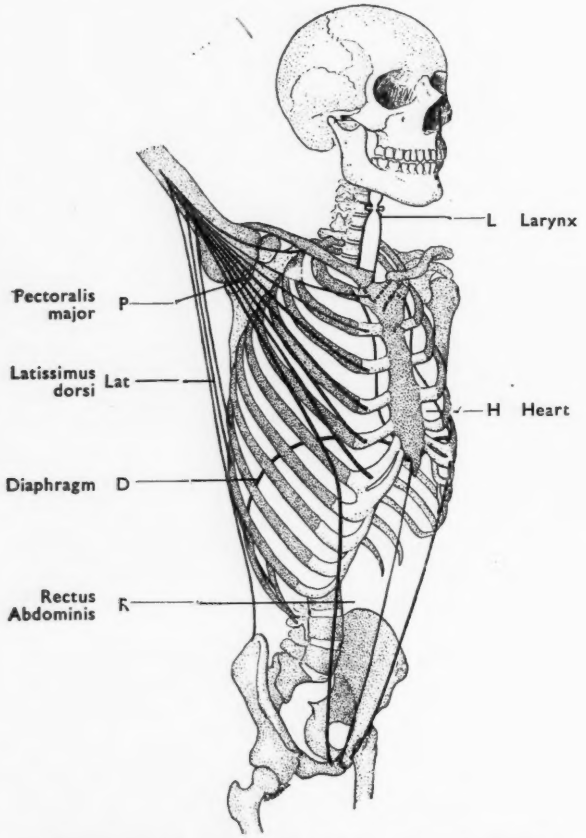


FIG. 187.—Diagram of human skeleton. Heavy lines indicate the pull of the pectoralis major, latissimus dorsi, and rectus abdominis. The figure is intended to show the tendency to elevation of the ribs during forelimb efforts and the assistance of the larynx in preventing entry of air into the lungs, thus resisting expansion of the thoracic cage. (*From "Journal of Laryngology and Otology"*, 1924, January.)

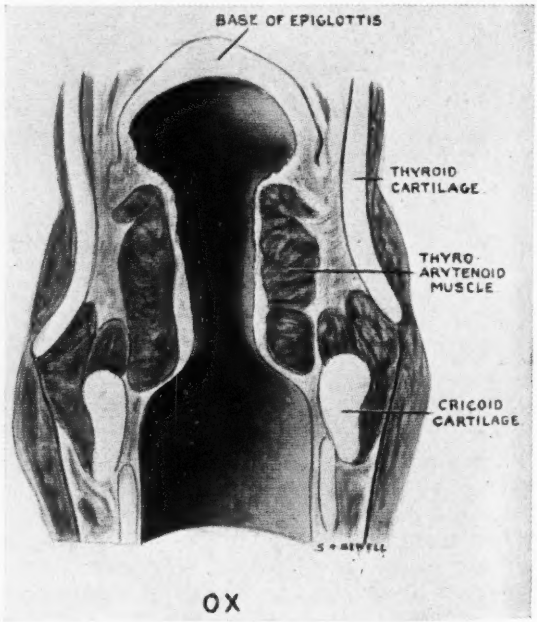


FIG. 188.—Section of larynx of an ox (*Bos*). There is no mechanical valve, but only a muscular sphincter.

direction upward and forward towards the hyoid bone and mandible (*see Figs.* 180, 197 B.) As the larynx rises, its aperture is closed by contraction of the sphincteric girdle of muscles, notably the thyro-arytenoid, the ary-epiglottic, and the inter-arytenoid;

the last passes under the recurved cartilages of Santorini, which are tilted forward. The anterior wall of the œsophagus is attached to the tips of these cartilages and as the cricopharyngeal sphincter is relaxed during this action, there is consequently wide opening of the mouth of the œsophagus in a funnel-like manner (*Fig.* 190); closure of the larynx and opening of the œsophagus are thus carried out by a simultaneous muscular process.

In man, the œsophagus is partially attached, also, to the back of the cricoid cartilage (*Fig.* 191); the opening of the mouth of the œsophagus is therefore slightly more restricted than in most mammals, in which the corniculate cartilages are large and well formed, affording the sole support of the anterior wall of œsophagus and allowing of a wide range of movement (*Fig.* 192).

In dogs the mechanism is very efficient, since fibres of the thyro-arytenoid muscle pass backwards

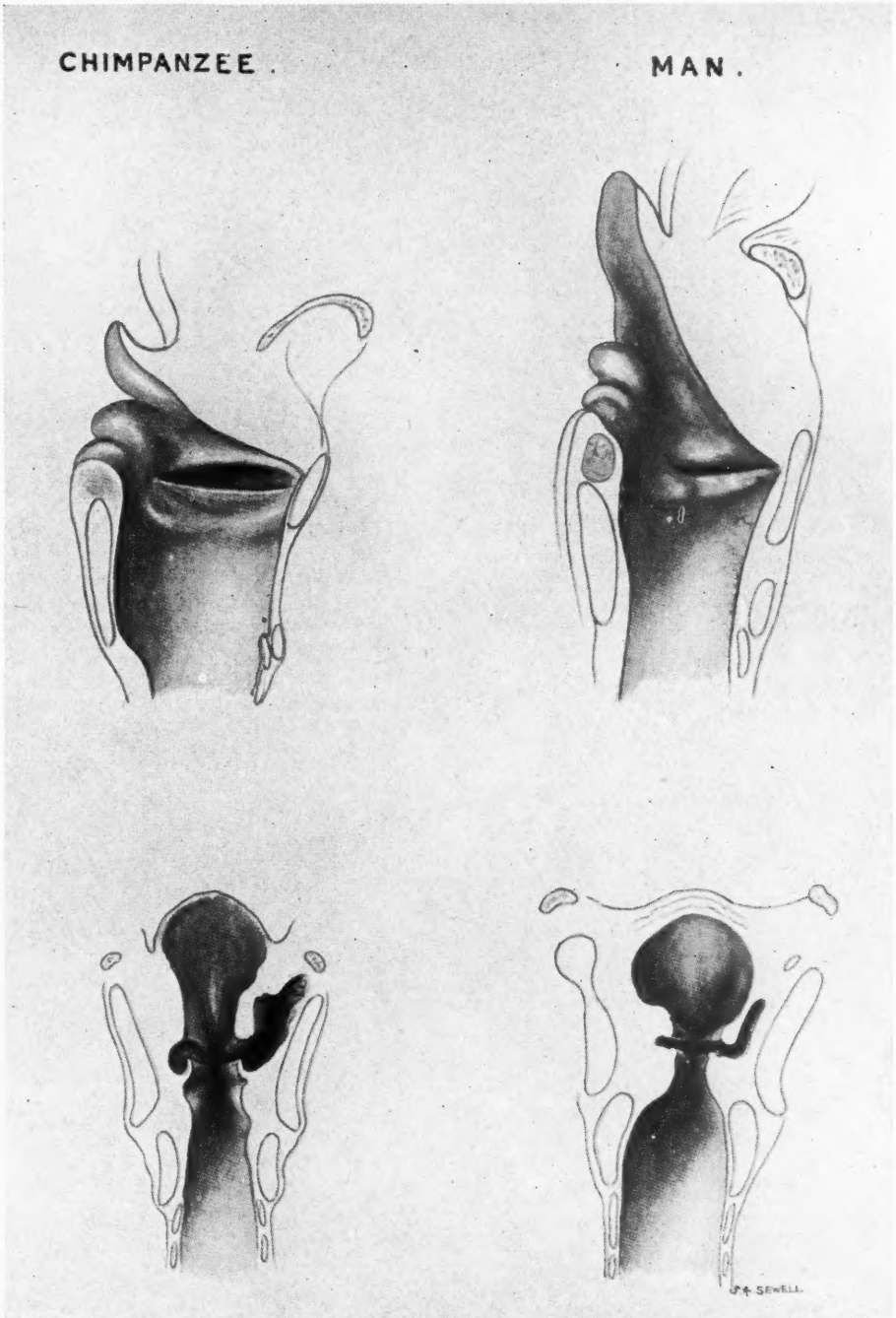


FIG. 189.—Sagittal and coronal sections illustrating the comparative efficiency of valvular inferior thyro-arytenoid folds or inlet valve of man and chimpanzee; the exit valve, provided by the ventricular band, is also seen. (*From "Acta Oto-laryngologica"*, 1928, 12.)

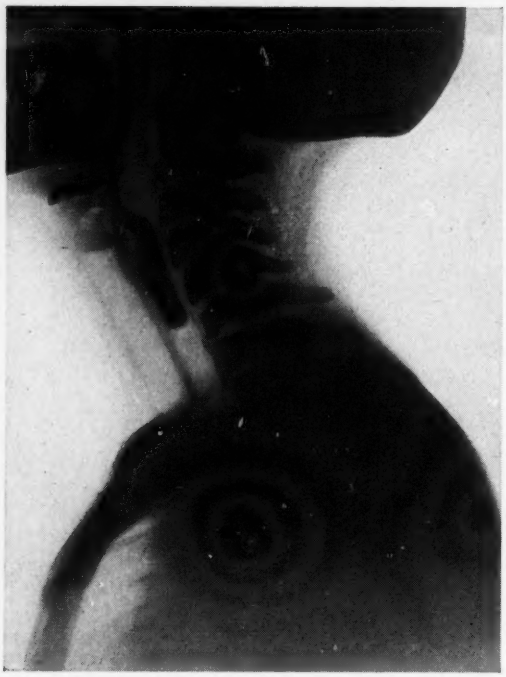


FIG. 190.—Radiograph to show the funnel-shaped opening of the œsophagus during swallowing. The larynx, and with it the anterior wall of the œsophagus, have moved upwards and forwards with the hyoid bone towards the mandible. The cricopharyngeal sphincter is relaxed. (*Radiograph kindly lent by Dr. T. V. Crichlow.*)

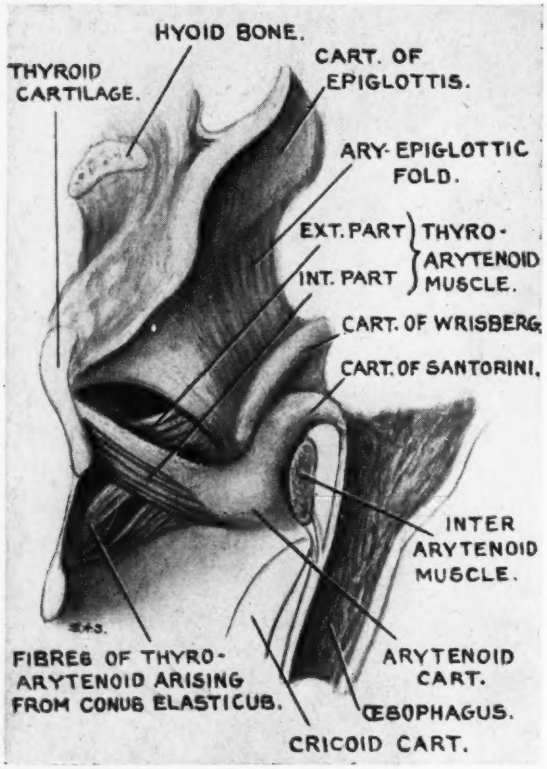


FIG. 191.—Dissection of right half of larynx of a *man, aged* 50. The cuneiform cartilage of Wrisberg is seen supporting the ary-epiglottic fold. The recurved corniculate cartilage of Santorini gives attachment to the anterior wall of the œsophagus; the latter is attached also to the back of the cricoid cartilage.

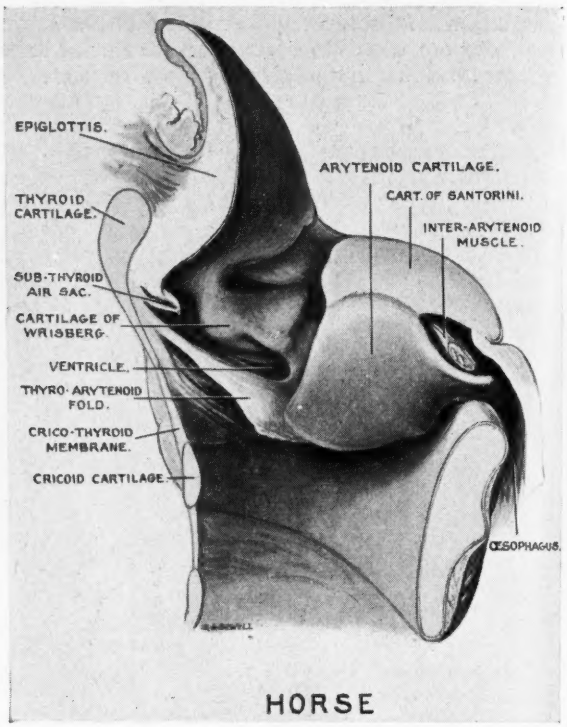


FIG. 192.—Dissection of right half of larynx of a horse (*Equus*), to expose the big cuneiform cartilage of Wrisberg, joined to the median region of the epiglottic cartilage, and also the big cartilage of Santorini, giving suspension to the œsophagus.

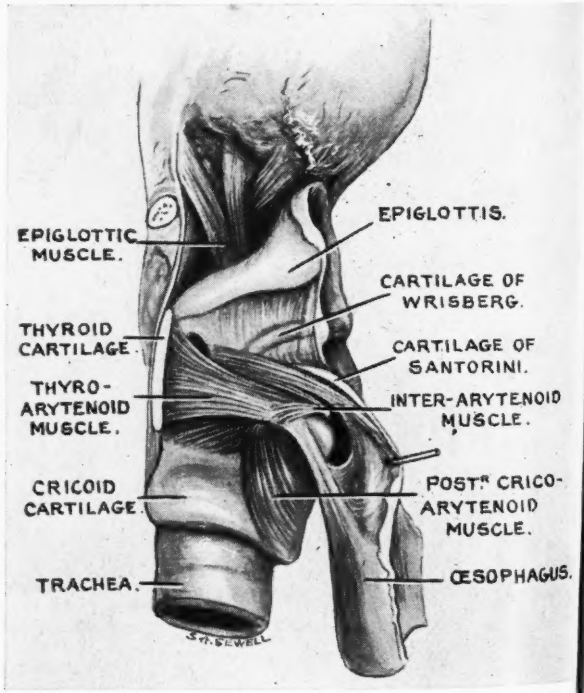


FIG. 193.—Continuity of longitudinal fibres of œsophagus with thyro-arytenoid muscle in a dog (*Canis familiaris*). The dissected larynx is viewed from the left. The cartilage of Wrisberg helps to support the ary-epiglottic fold, and below and behind it a long process of Santorini gives support to the œsophagus, which is held back by a hook. (*From "Journal of Laryngology and Otology"*, 1925, November.)

and downwards to blend with longitudinal fibres of the œsophagus (*Fig.* 193).

It is to be noted that the pull on the œsophagus is directed mainly to the anterior wall. Man, in particular, has stylopharyngeal and palatopharyngeal muscles which terminate before reaching the mouth of the œsophagus, with consequent lack of elevation of the posterior œsophageal wall. The œsophagus, being fixed below the diaphragm, unlike the trachea which is free to rise within the thorax, exerts a downward pull and tends to increase the gap between the circular and oblique fibres of the inferior constrictor during swallowing.

Influence of a Herbivorous Diet.—Carnivora, such as members of the cat tribe, have a fairly simple type of larynx which closes as a bolus passes into the œsophagus. I have never found a diverticulum of the pharynx in animals of this type.

Herbivora, on the other hand, have a more complicated anatomy, to enable them to swallow large quantities of semi-liquid herbage without the necessity of arresting respiration. The possibility of simultaneous respiration and deglutition is attained by separation of the air- and food-passages, by the intermediation of an arcus palatopharyngeus (*Fig.* 194). This is a fold of mucosa enclosing fibres of the palatopharyngeus muscle, surrounding the aperture of the larynx and continuous in the posterior direction. The larynx is thus encircled and projects into the nasopharynx while respiration is carried on.

In association with this sphincter there is upraising of the lateral boundaries of the larynx in the form of ary-epiglottic folds. These folds extend from the epiglottis to the arytenoid; in many instances, where the arytenoid is small, they gain additional support from the presence of a cuneiform cartilage of Wrisberg (*Fig.* 195). Between the pharyngeal wall laterally, the ary-epiglottic fold medially, and the arcus superiorly, there is an efficient lateral food channel. Man, of herbivorous descent, has fairly high ary-epiglottic folds, but no arcus; his palatopharyngeal fibres, enclosed in the posterior pillars of the fauces, form the ridge of Passavant, but do not descend as far as the hypopharynx and do not form an encircling ledge or fold, nor do they reach the neighbourhood of the mouth of the œsophagus, as in herbivora, to give assistance to opening of the gullet during swallowing.

In those species with a well-formed arcus, the pump action of the tongue and pharynx against

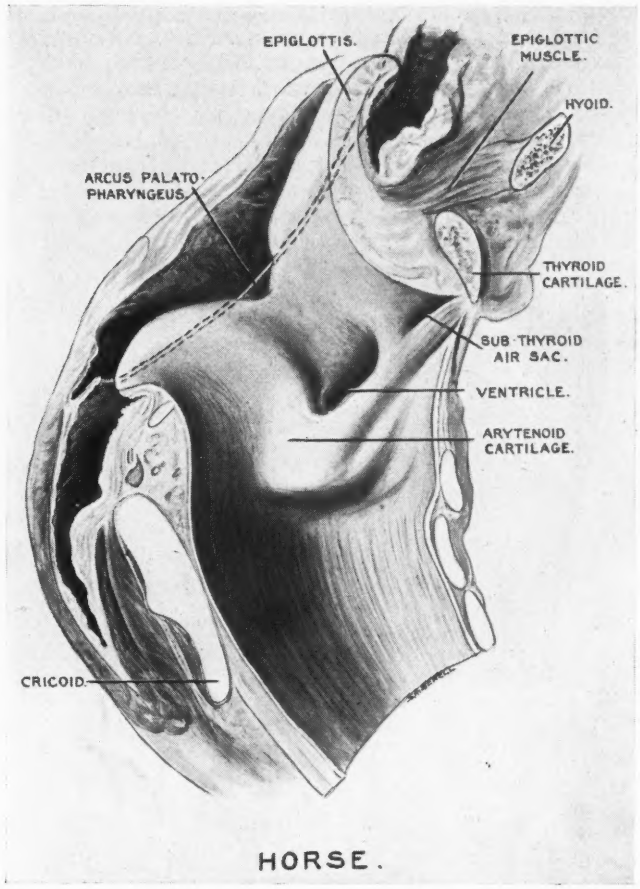


FIG. 194.—Left half of larynx of a horse (*Equus caballus*) to illustrate the position of the lateral food channel below the arcus and external to the high ary-epiglottic fold. (*Reproduced from "The Mechanism of the Larynx," by permission of Messrs. Heinemann.*)

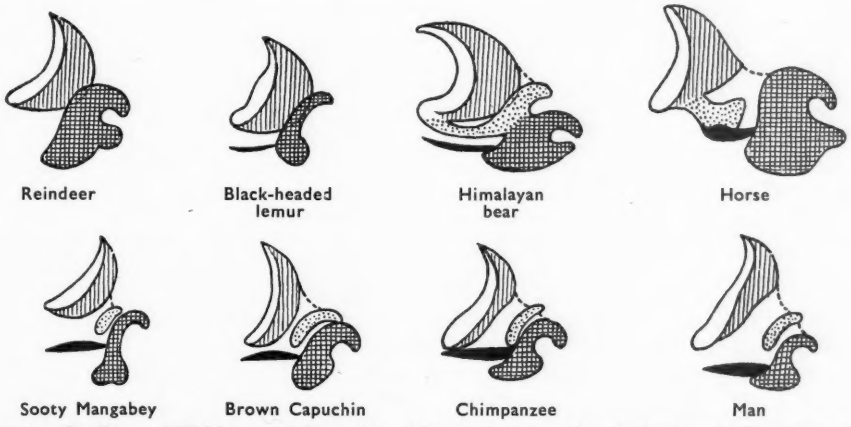


FIG. 195.—Cartilages of Wrisberg and Santorini. The epiglottic cartilage is lined vertically, the arytenoid and corniculate cartilages of Santorini are cross-hatched, while the cuneiform cartilage of Wrisberg is stippled. The Wrisberg cartilage appears in species with a small arytenoid, to support the ary-epiglottic fold.

the posterior pharyngeal wall is limited, the stream of food being directed into the mouth of the œsophagus; man, without an efficient lateral food channel, has no such accurate direction of food, a bolus being free to exert its pressure on any part of the hypopharynx.

Factors predisposing to Herniation.—An attempt has been made to describe the basic principles of deglutition and to point out the many factors which have arisen to complicate the anatomy and physiology of man. The human race has gained much from the assumption of the erect posture, from the addition of a large pharyngeal resonator for purposes of phonation, and also from separation of the soft palate and epiglottis, but by all these evolutionary changes man has rendered himself liable to certain disabilities, among which is the acquisition of a pharyngeal diverticulum.

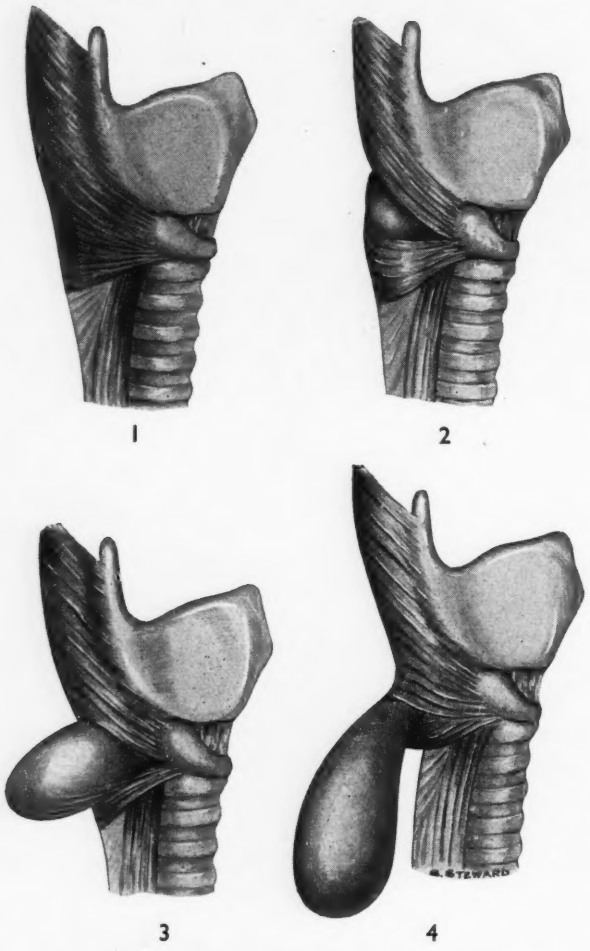


FIG. 196.—Pharyngeal diverticula. 1, Normal musculature of hypopharynx, showing the arrangement of inferior constrictor muscle. 2, Separation of circular and oblique divisions of the inferior constrictor (*Professor Parson's specimen, R.C.S., Eng.*). 3, Small pouch (*Mr. Colledge's specimen in Museum, R.C.S., Eng.*). 4, Large pouch (*R.C.S. Museum*).

The obliquity of the inferior constrictor and the horizontal direction of the cricopharyngeus cause an unsupported triangular area to be left in the posterior wall (*Fig.* 196). During swallowing the gap tends to become even more extensive, owing to the upward movement of the pharynx and larynx. The palato- and stylo-pharyngeus muscles terminate in the lower pharynx and no vertical fibres reach the œsophagus. The latter, being anchored to the diaphragm, exerts a downward pull, which has greater effect on the posterior than on the anterior wall, since the latter is suspended from the larynx.

When one studies the anatomical and physiological details, it is surprising to find how few suffer from herniation.

To recapitulate, the factors referred to are, particularly: (*a*) the low position of the larynx, and with it the descent of the mouth of the œsophagus; (*b*) the obliquity of the inferior constrictor muscle in relation to the circular arrangement of the cricopharyngeus; (*c*) the attachment of the anterior wall only of the œsophagus to the larynx and its wide range of movement during swallowing; (*d*) the active contraction of the cricopharyngeal sphincter and the difficulties of co-ordination of its relaxation with contraction of the pharyngeal force pump; (*e*) the lack of longitudinal suspension of the posterior wall of the mouth of the œsophagus; and (*f*) the absence of support at an unprotected spot.

But it is not everyone who acquires a pouch. Consequently we can exclude those anatomical factors which are common to all; these are (*a*), (*b*), (*c*), (*e*), and (*f*). The physiological factor of variable influence is obviously (*d*), the co-ordination of relaxation of the sphincter.

Reasons for Appearance of Bulging in the Triangular Gap.—At the beginning of the communication it was assumed as an axiom that a pouch in its early stages is the result and not the cause of dysphagia. Bulging in the weak triangular area may be brought about in several ways; this bulge may be followed by herniation and the formation of a pouch.

a. Chronic inflammation at the cricopharyngeal fold, best known as chronic hypopharyngitis in my opinion, can be seen in certain cases if direct examination be made. The presence of inflammation leads to lack of relaxation of the sphincter; relief is afforded by dilatation, repeated when necessary. In one case a pouch the size of a little finger-tip was present, but with apparent disappearance after dilatation on two occasions (*Fig.* 199). A minority of patients have, in addition, superficial glossitis, and a still smaller proportion suffer from microcytic anæmia. If all three conditions are present they are said to show the Plummer-Vinson syndrome, which is described more accurately under the names of Paterson and Brown Kelly. Patients suffering from chronic hypopharyngitis require, in addition to dilatation, large doses of iron. The progress of early herniation may be arrested by the treatment suggested.

b. Healed inflammatory lesions of the cricopharyngeal fold lead to contraction and stenosis at the mouth of the œsophagus, with dysphagia and sometimes the formation of a pouch (*see Fig.* 200). Dilatation alone should relieve symptoms. I have seen cases where the process was in its early stages, with a broad depression behind a tight cricopharyngeal fold.

c. Many patients have excessive contraction of the sphincter, without any obvious pathological

cause. Wide stretching of the cricopharyngeus with a hydrostatic bag gives relief and may counteract or delay the formation of a pouch. Similar treatment is applied to other sphincters of the body with good effect.

d. Lack of relaxation at the right moment in the second stage of swallowing may be due to deficiency in the sensory stimulus, which originates in the posterior pharyngeal wall from the impact of food. This may be caused by partial atrophy of the mucosa or may be present without obvious reason. The reflex arc comes through the pharyngeal plexus to the vagal fibres which relax the sphincter. The motor cells from which these fibres originate are situated in the nucleus ambiguus of the spinal accessory nerve. They leave the skull in that nerve and pass, after leaving the jugular foramen, to the ganglion nodosum of the vagus via the internal branch of the accessory.

e. Sympathetic fibres from the superior cervical ganglion reach the cricopharyngeal sphincter. They have been divided by Lambert Rogers in an attempt to paralyse the sphincter, in the belief that they supply the pressor element. Mr. Last points out that the sphincter consists of striped muscle and that a sympathetic nerve-supply cannot be assumed to have any motor function.

Reasons for Dysphagia.—The muscular wall of the pharynx rests on areolar tissue, which separates it from the prevertebral fascia. Normally the posterior wall of the pharynx lies flush on the front of the prevertebral fascia and cannot travel farther backwards because of the resistance of the vertebral column (*Fig.* 197 A). The bulge referred to is caused by pulling forward of the posterior or pharyngeal wall by muscular action above and below the triangular area deficient in muscle-fibres (*see Figs.* 180, 196, 197 C,) ; that is to say, the pull of contracting oblique fibres of the inferior constrictor above and of incompletely relaxed cricopharyngeal fibres below the weak area. Gradual stretching of the areolar tissue leads to the formation of a bulge which, later,

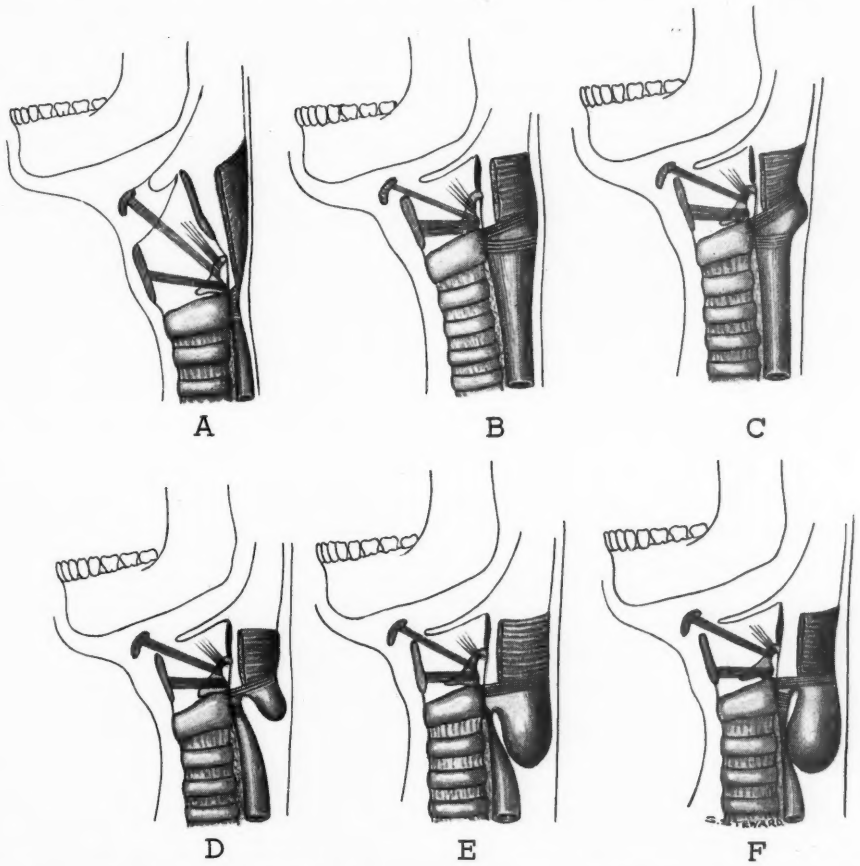


FIG. 197.—Diagrammatic representation of the production of a pouch. The figures illustrate the movements of the larynx and mouth of the œsophagus during swallowing. A, Normal position during respiration. The larynx is low and its sphincteric muscles are relaxed. The mouth of the œsophagus is closed by the cricopharyngeus, which pulls the posterior pharyngeal wall slightly forwards ; the constrictors are relaxed. B, During the second stage of swallowing the larynx is pulled upwards and forwards to the hyoid, and the latter travels in a similar direction nearer to the mandible. The constrictors then execute a peristaltic wave and the mouth of the œsophagus opens in a funnel-like manner to allow the bolus to pass (*see Figs.* 180 B, 190). C, Shows the effect of inefficient relaxation of the cricopharyngeus. The bolus is delayed in its passage. In consequence the posterior pharyngeal wall is pulled forward both above and below the unsupported triangular area, which bulges, owing to the force-pump action of the constrictors. D, Food squeezed into this bulge gradually excavates a small, broad pocket behind the cricopharyngeal fold, which is no longer closely applied to the prevertebral fascia. The opening into the œsophagus is still in the vertical plane, while that into the commencing pouch is oblique. E, The pouch is now well formed ; the posterior wall of the cricopharyngeal fold rests against the back of the cricoid cartilage and moves upwards and forwards with the larynx during swallowing. The opening into the œsophagus is now directed obliquely, while that into the pouch is vertical. F, The large pouch now causes dysphagia by pressing on the œsophagus when filled.

by the entrance of food, may be enlarged to form a hernia and eventually a pouch (*Figs.* 196, 181, 197 D).

The pathological process will come about if both the oblique fibres of the inferior constrictor and cricopharyngeus contract synchronously while a

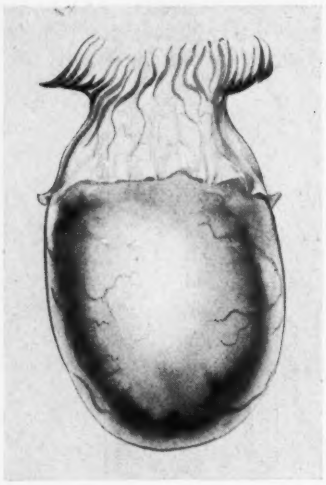


FIG. 198.—Drawing of a pouch with its neck exposed and with a cuff of pharyngeal aponeurosis and muscle-fibres separated from the mucosa, which is still intact.

bolus of food is in the hypopharynx. The bolus cannot move forward because of the resistant larynx, nor laterally owing to resistance of the inferior constrictor; its upward passage is resisted by the contracted inferior constrictor, while downward movement is made difficult or impossible by closure of the mouth of the œsophagus. The posterior gap takes the force of this combined contraction and bulges.

Now as soon as the posterior wall of the hypopharynx is separated from the prevertebral fascia, to which it is normally held by atmospheric pressure, the opening of the mouth of the œsophagus is disturbed. For when the larynx moves upward and forward during deglutition, it carries with it not only the anterior wall of the œsophagus, as it should, but the posterior wall also (*Fig.* 197 E). Even if the sphincter were relaxed, there would be nothing to hold back the posterior wall if an excavation were present behind it. This means that the normal funnel-like opening of the mouth of the œsophagus, designed to receive a bolus of food, is absent; the bolus therefore impinges on the posterior wall, with further enlargement of the hernia.

In its early stages the pouch itself cannot produce dysphagia, as it is not of a size to press on the œsophagus; when it becomes very large and descends into the superior mediastinum it may have a direct effect by its pressure when filled, in the relatively narrow thoracic inlet (*Fig.* 197 F).

Anatomy of Pouch.—To adopt correct lines of treatment, it is necessary to have a clear understanding as to the formation of a pouch.

Internally is the mucous membrane, which may in certain instances be inflamed; next is the aponeurosis of the pharynx, that firm layer which is best seen during dissection of tonsils. External to and attached to the aponeurosis are the longitudinal and circular muscles, in that order; and outside the muscle-fibres is the buccopharyngeal fascia, adherent sometimes when the pouch descends into the mediastinum.

The muscle-fibres are spread out over about one-third of a large pouch, in most cases, and fade away as they leave the neighbourhood of the pharynx; they are, however, quite obvious (*Figs.* 196, 181). By careful dissection it is possible to separate the outer layers, even as far as the mucosa, which then remains as a thin sac surrounded by a cuff of fused fascia and muscle-fibres (*Fig.* 198); this dissection will be referred to later as an important step in the operation.

TREATMENT OF A DIVERTICULUM

Symptoms are characteristic and diagnosis is straightforward, but having decided that a pouch is present, an essential step is direct examination with an œsophageal speculum. The evidence to be obtained is first the size and depth of the diverticulum; its mouth is easily found and appears as a wide opening behind the cricopharyngeal fold. The mouth is not circular, as it appears in lateral radiographs, but extends right across the width of the hypopharynx. The state of the wall is examined

FIG. 199.—Very small diverticulum in a female. Dysphagia was relieved by dilatation of the cricopharyngeal fold, which was affected by mild chronic hypopharyngitis. No evidence of a pouch was present after two dilatations.

for evidence of inflammation or possible malignant changes. The mouth of the œsophagus is then sought, and may be difficult to find; it opens obliquely on the posterior surface of the cricoid cartilage. In view of what has been said above, it

is obvious that when the larynx is lifted forward with the beak of the speculum, the whole œsophagus moves forward, there being no force to hold back the posterior wall. But usually, by movement of the

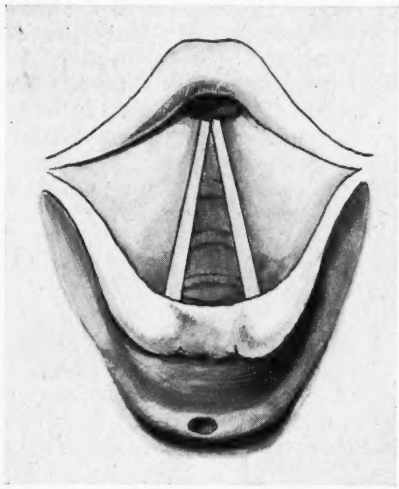


FIG. 200.—Cicatricial stenosis of mouth of œsophagus due to healed chronic hypopharyngitis. Organic obstruction of this type may lead to herniation; a depression is seen posteriorly.

speculum or by gentle exploration with a gum-elastic bougie, the œsophageal opening is found; if there be great difficulty, relaxation with curare will solve the problem.

a. In the case of a very small pouch, wide dilatation of the sphincter with a hydrostatic bag may be all that is required; repetition may be necessary after a few months, dependent on the evidence of symptoms and radiography (*Fig.* 199).

b. If chronic hypopharyngitis is present, dilatation is carried out and is repeated after, possibly, one month; iron is given if indicated (*Fig.* 199). Powders of barium sulphate, 3 gr., to protect any ulcerated surface, with orthocaine, 1 gr., to relieve discomfort and facilitate relaxation, are swallowed without water three or four times daily, twenty minutes before meals.

c. If cicatricial scarring with stenosis is found, dilatation must be gradual for fear of excessive tearing of the mucosa. Repeated treatment, two or three times, at two- to three-week intervals, may be required to relieve dysphagia and to attempt to arrest enlargement of the pouch (*Fig.* 200).

d. The cricopharyngeus is reported to be relaxed by division of its sympathetic nerve-supply, as mentioned above. But this operation, if its effects were lasting, might well be followed by œsophageal respiration, with ballooning of the œsophagus and elimination of peristalsis, subsequently leading to symptoms of what is generally called cardiospasm.

e. After exposure of the pharynx and œsophagus from without, and after freeing the sac and displacing it upwards, it would be possible to divide the cricopharyngeal fibres (*Fig.* 201 B). If the muscle were put completely out of action, air swallowing and ballooning might result. The operation would be almost as difficult as complete removal of the pouch, and would be no more safe.

f. Division of the spur or party wall between pouch and œsophagus has been adopted as a means of treatment (*Fig.* 201 A). Mosher (1917), and Seiffert (1937) used biting forceps and Dohlman (1950) has employed electrocoagulation. The cricopharyngeus would be cut through by either method. This operation appears precarious theoretically, and we prefer to adopt an external operation for removal of the pouch without undue danger.

g. Diverticulopexy, or slinging up of the sac, was suggested by Schmid (1912) and adopted for use by Hill (1918). The sac is exposed, freed from its connexions, and is then attached to the lateral wall of the pharynx, upside down (*Fig.* 201 C). The idea is that no food will enter and therefore there will be no symptoms. It is obvious, however, that nothing has been done to strengthen the wall of the diverticulum; that part just above the cricopharyngeus will still receive the impact of food and will sag downwards, to re-establish at first a shallow recess and later a fully formed sac. On theoretical and practical grounds this operation does not appear to have merit.

h. Removal of the sac and closure of the neck is the method usually adopted. The operation can be carried out in two stages, with isolation of the pouch as the object of the first step (*Fig.* 201 B), and its removal as the second step. The problematical danger of mediastinitis does not seem to be a sufficient reason for prolonging the treatment, for

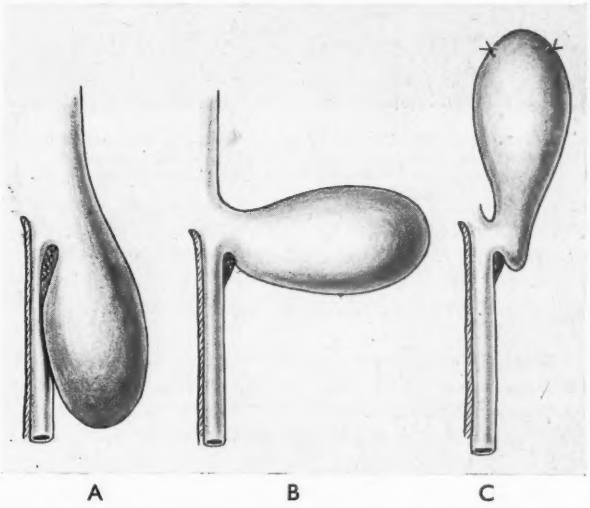


FIG. 201.—A, Shows a pouch lying against the œsophagus; some surgeons have divided the party wall between the two. B, The pouch has been freed from its bed; the cricopharyngeus is seen in section and could be divided. C, The freed pouch has been elevated and attached to the pharynx; the weak area above the cricopharyngeus is still present, with a probability of recurrence.

subjecting the patient to a second operation, or for making firm repair of the pharyngeal defect more difficult than if carried out primarily.

i. Removal in one stage is to us the method of choice when it is decided that operation is required. With attention to certain details, to be described later, the operation has no great technical difficulties and does not entail any undue danger. Repair should be so firm that recurrence is prevented.

In one or two earlier cases, where a very large pouch lay in the mediastinum, we have encountered infection of the resulting cavity; drainage put matters right without any signs of diffuse mediastinitis. Many patients subjected to lateral pharyngotomy for malignant growths, are left with a leaking

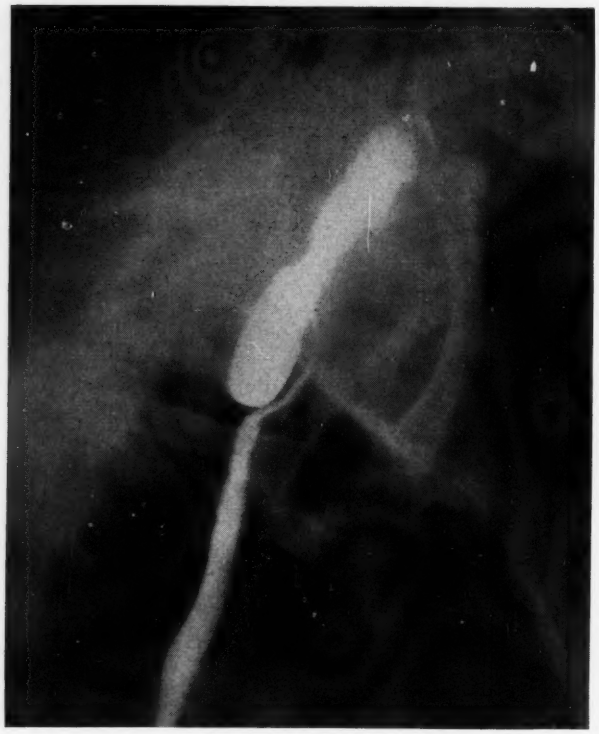


FIG. 202.—Medium-sized pouch in a middle-aged man, removed by a one-stage operation without any complication. The relation of the œsophagus to the diverticulum is well shown.

pharyngostome but with no evidence of mediastinitis. Even before the prophylactic use of sulphonamides and penicillin danger was slight, and since their adoption it is, in our experience, negligible.

Optimum Time for Removal of a Pouch.—In consideration of the possible arrest of herniation by dilatation, there should not, in my opinion, be any immediate decision to operate on a pouch made visible by radiography.

The opening into the diverticulum is not circular; it is wide and usually as broad as the hypopharynx, at first more like a deep recess than a sac. Later a neck is pulled out, but even then the transverse diameter is greater than the anteroposterior.

With a very small sac it is difficult to find sufficient material to close the defect so firmly that it becomes the most resistant, instead of the feeblest, area in the hypopharynx. It is probably wise, therefore, to delay operation with very small sacculations, and if the remarks above are correct, it may be found that dysphagia can be allayed by dilatation and that evolution of the pouch may be arrested (*Fig.* 199).

When a pouch reaches the mediastinum, operation is required, and the sooner the better (*Figs.* 202, 203), except with very old patients, such as those who have reached the age of 80.

Preliminaries to Operation.—The teeth must be devoid of infection. Direct examination should be made, at least a few days before operation; the cricopharyngeal sphincter is stretched widely.

The pouch should be emptied by the insertion of a catheter, preferably coupled to a suction pump, the day before operation, or sooner and more often if the sac is inflamed.

When the patient has been anæsthetized, insertion of the speculum allows the sac to be completely emptied. The aperture of the œsophagus is then found and a long, fine feeding tube is inserted; the upper end is withdrawn through the nasopharynx and nose by means of a catheter inserted through the wider nasal fossa.

An important step is then carried out; this is packing of the pouch with a long strip of ribbon gauze soaked with 2 per cent mercurochrome, which acts as an antiseptic and also distends and outlines the pouch to facilitate dissection (*see Fig.* 198).

Technical Details of Operation.—A long vertical incision, usually on the left side, is employed; the pouch is defined and brought up from the mediastinum. Mr. C. P. Wilson has emphasized to me the advantages of dividing the superior thyroid artery, if necessary, so that the whole larynx can be rotated; exposure of the pouch and repair of the defect is thereby facilitated.

In order to protect the contents of the carotid sheath from infection, should leakage subsequently

FIG. 203.—Very large pouch in a female, aged 49. One-stage operation with normal swallowing after 14 days and with no subsequent symptoms. Barium is seen in the valleculæ.

occur after removal of the sac, part of the sternomastoid muscle is freed and sewn over the sheath to the prevertebral fascia. Protective packs are placed in the thoracic inlet. By gentle dissection the muscular and aponeurotic layers of the wall are separated like a cuff from the mucosa as far as the

pharyngeal wall, exposing the neck where it joins the hypopharynx. A transverse continuous inverting suture is inserted into the mucosa, and when it is in position the sac is amputated and closed; other interrupted sutures are tied, if required, in such a way as to cause infolding of the mucous membrane. The layers of aponeurosis and muscle are then brought over the stump in a double-breasted manner, to ensure complete closure and firm repair. Care is taken to avoid a tight scar, with the chance of stenosis; the presence of the feeding tube during the operation is a guide to the right level of closure.

FIG. 204.—Radiograph of a man, aged 38, who had a very large diverticulum removed by a one-stage operation. Swallowing of barium 13 months after operation showed insufficient relaxation of cricopharyngeus, with temporary delay of bolus and the formation of a slight shelf. Dilatation of the mouth of the œsophagus was therefore carried out.

Having dusted the wound thoroughly with penicillin and sulphathiazole, a further detail is the insertion of two or three catgut sutures to keep the posterior wall of the pharynx, and with it the attachment of the cricopharyngeus, temporarily in contact with the prevertebral fascia, after making sure that the parts have been restored to their correct position without twisting or kinking.

The wound is left open in accordance with the advice of Trotter, with a tube leading down to the mediastinal recess, while a broad corrugated drain keeps the pharynx and carotid sheath apart. The wound is kept open for at least six days, until it gradually closes from below; the subsequent scar is remarkably inconspicuous. This method may be over-cautious, but it appears advantageous when the one-stage operation is employed.

After-treatment.—Penicillin is given for three days, and sulphathiazole for five days in the usual case. The feeding tube is retained for about nine days to allow firm healing to proceed and to ensure re-apposition of the cricopharyngeus and posterior pharyngeal wall in their normal position against the prevertebral fascia.

In about six weeks it is best to watch the swallowing of thick barium; if there is any delay, direct examination and dilatation of the mouth of the œsophagus are carried out.

Except for the inconvenience to the patient, post-operative dilatation is a useful preventive of subsequent difficulties, and is a procedure I usually carry out (*Fig.* 204).

CONCLUSION

To many this lengthy dissertation may appear tedious and superfluous. They may feel that operative results are so good as to require no improvement. But in my experience several unfortunate sequelæ to operation have impressed on me the desirability of comprehending the aetiology and evolution of pharyngeal diverticula in order to avoid failure.

I myself have encountered several cases where recurrence of the pouch has occurred, or where dysphagia has continued after operation; I believe that these failures can be avoided.

I am particularly indebted to Sir Arthur Keith for his early description of the cricopharyngeal sphincter; and to Dr. Chevalier Jackson for his repeated insistence on its importance. A basic knowledge of this subject is essential to an understanding of the aetiology of pharyngeal diverticula.

I wish also to express my gratitude to Mr. R. J. Last, Mr. Daggett, and Mr. Roland Lewis for their kindly and useful criticism of this paper.

Several of the illustrations are reproduced from the author's *The Mechanism of the Larynx* (1929) and *Comparative Anatomy and Physiology of the Larynx* (1949), by permission of the publishers, Messrs. Heinemann.

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FIBROADENOSIS

By H. J. B. ATKINS, London

Some years ago I defined fibroadenosis as a " painful or nodular condition of the breast, not due to new growth, bacterial inflammation, or fat necrosis " ; an unsatisfactory, negative sort of definition, but one upon which, in the intervening years, I have been unable to improve.

The material upon which the present study is based comes from the Mastitis Clinic at Guy's Hospital which was started in 1936. At that time we used the term ' chronic mastitis ' to describe this condition, but for reasons which have been set out at length (Atkins, 1947) we prefer the term ' fibroadenosis ' as being adequately descriptive, euphonious, and precise. When we discarded the name chronic mastitis we retained the name ' Mastitis Clinic ' because, by that time, we were seeing a large number of cases of advanced carcinoma in addition to cases of fibroadenosis, and the name of the Clinic was suitably non-committal and did not serve to frighten away potential patients. Since its inception 326 cases have been studied. The war interrupted the work, and made the follow-up of our cases somewhat incomplete. Nevertheless, of 187 cases seen before the war 116 have been followed up.

Our studies have been both clinical and histological, and from time to time different methods of treatment have been assessed using both clinical and histological criteria. In the evaluation of any therapeutic measure we have been at pains to have adequate controls, bearing in mind that the anxiety associated with this disease is a predominant feature, and that if anxiety is relieved, a high proportion cease to bother about their symptoms. Thus without controls too favourable an impression may be obtained as to the value of any therapeutic measure which is being tested.

At the stage when we were investigating specific therapeutic measures, it was our practice to make a clinical assessment of the condition before treatment was begun, and to take a biopsy. At the conclusion of the treatment a further clinical assessment was made, and a further biopsy taken, and a series of such findings was compared with a parallel series treated in every respect similarly, but in which the specific medicament had been withheld. To make this effective, recourse was had to such expedients as the injection of sterile olive oil and the prescription of chalk pills in the control series. The results of these experiments have been described elsewhere (Atkins, 1949), and will be discussed below. Latterly, when no specific remedy was being investigated, new cases were examined and a biopsy was taken, the patient being told to report at regular intervals. As a result of an examination of our material in this way we have been able to relate physical signs to microscopical appearances more precisely than had been possible hitherto. Abnormal signs on palpation are classified as :—

1. *Granularity* when the discrete firm masses are less than a few millimetres in diameter ;

2. *Nodularity* when these masses are half a centimetre to a centimetre in diameter ; and

3. *Lobularity* when they are larger than this.

The term ' nodularity ' is also used in this paper as a general term to cover all these abnormalities when there is no purpose in discriminating between them.

In discussing the histological changes of fibroadenosis we will try to interpret the different histological pictures which are obtained in terms of these qualities.

Fibroadenosis, by definition, is a painful or nodular condition of the breast ; but most women get some pain in the breast from time to time, and the vast majority of breasts are more nodular than the surrounding subcutaneous tissue. Are we then to say that the majority of women suffer from fibroadenosis ? If not, what degree of pain or nodularity are we to regard as abnormal ? Here we come at once to the crux of the whole problem. Speaking in a clinical sense, no hard-and-fast line can be drawn between what is physiological and what is pathological ; fibroadenosis is in fact a disease without a ' beginning point '.

Early in the history of the Mastitis Clinic I took a number of patients who were attending the Clinic, discarding those with a localized lump, and using only those with a diffuse nodularity (M), and an equal number of female patients of a similar age who were in hospital for some disease unassociated with the breast (C). I asked the then senior surgeon to the hospital, Mr. E. C. Hughes, to range these patients in what he considered to be an order of severity as far as nodularity was concerned, and this was the order :—

M, C, M, M, C, C, C, C, M, M, M, C, M, C,

as haphazard a grading as my experience had led me to expect.

This is not to say that those who *complain* have not, by and large, a greater degree of nodularity than those who do *not complain*, and some of the former have a localized lump which must be considered an abnormal physical sign. Nevertheless, the borderline between normality and abnormality is an indefinite one, and such a conception must be borne in mind when considering such important matters as the possible precancerous tendency of this disease, a problem which is discussed in detail below.

HISTOLOGY

Let us now consider the histological appearances obtained in biopsy material from women who suffer from fibroadenosis. These may be grouped broadly under three headings—epithelial, cystic, and mesenchymal.

1. Epithelial.—These changes are essentially proliferative, and have been conveniently differentiated by Dawson (1934) into two types, adenosis and epitheliosis.

a. Adenosis consists in the multiplication of epithelial systems, such that in any microscopical field there appears to be a larger number of these than would be considered normal. *Fig.* 205 may

be regarded as normal; *Fig.* 206 as representing adenosis. It should be explained, as Dawson has pointed out, that to talk of 'alveoli' or 'acini' in and brings this point to light. These authors, in describing the histology of the walls of the ducts, say that the elastic lamina usually stops short at the

FIG. 205.—A his tological picture which may be regarded as 'normal'. (× 120.)

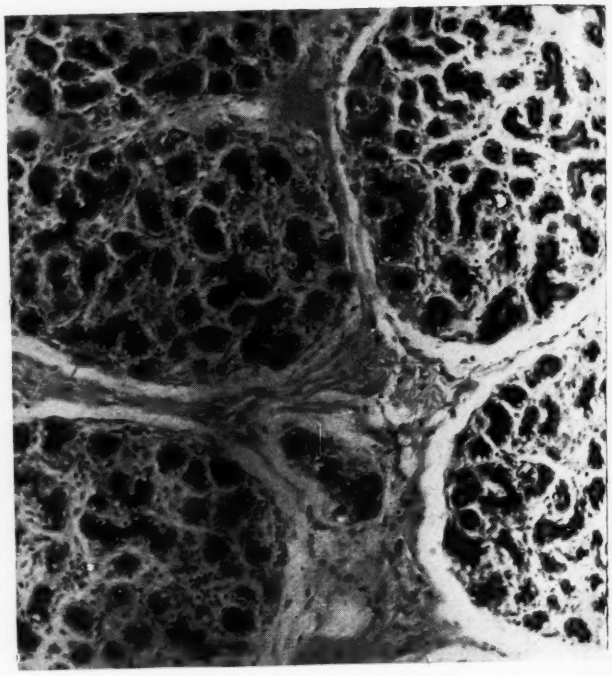

FIG. 206.—Adenosis. (× 120.)

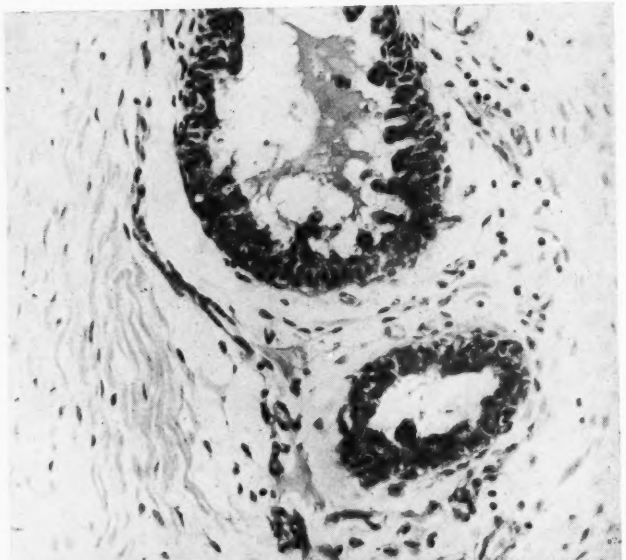

FIG. 207.—Early epitheliosis. (× 250.)

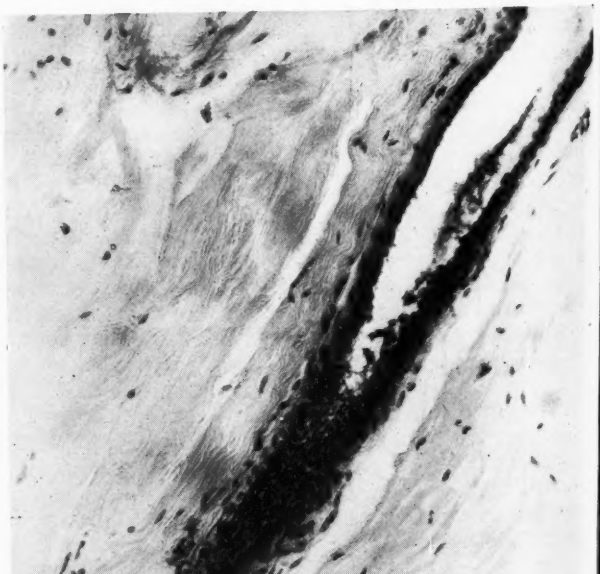

FIG. 208.—False appearance of epitheliosis due to oblique section of a duct. (× 250.)

a non-lactating breast is to stretch the implications of these terms too far. A careful perusal of that great descriptive work *Tumours of the Breast* by Cheatle and Cutler (1931) reveals the same difficulty, junction of duct and alveolus; in defining an alveolus (as distinct from a duct) they say that an alveolus is that part of the epithelial system which is devoid of an elastic lamina! An alternative to

describe the terminal branches of the ducts in the non-lactating breast would be the term ' ductule ', and an aggregation of them, as seen on section, a ' ductular system '. Nevertheless, if the fight for the adoption of the term ' fibroadenosis ' is won, this point, which assumes importance only in the problem of the origin of breast cancer, may be conceded for the time being, and we will talk of the termination of the ducts as alveoli, although they do not secrete.

If the clinical differentiation between what is normal and what is abnormal is difficult, how much more so is this the case with the phenomenon of adenosis? Who is to say how many alveoli per square millimetre of cross-section of breast tissue is to be regarded as normal for any particular age or physiological state of the breast?

b. Epitheliosis.—Whereas the alveoli multiply, the epithelial cells lining these alveoli and the epithelial cells lining the ducts also undergo proliferative changes, and to these changes the term ' epitheliosis ' is applied.

In describing the changes of epitheliosis every author, so far as I am aware, begins by describing slight changes, passes on to more striking changes, and concludes with a description of the most florid changes on the tacit, and in some instances the declared, assumption that the one passes on into the other in an orderly and pre-ordained sequence. This may be so, but it is not necessarily so, and there is certainly no evidence for it. If, therefore, we follow the same order because it is simpler for the purpose of description, we must not assume that this order is a sequence; stage vi may appear without the intervention of stages v and iv, without even the intervention of stages ii–v inclusive.

In the breasts of women who have complained of no symptoms, the ducts and alveoli are commonly lined by columnar or cuboidal epithelium two rows deep; we will therefore regard this as normal. Epithelial proliferation takes many forms, of which the ensuing are frequently encountered.

i. The cells lining the ducts and alveoli multiply so that instead of being two rows thick they are three or more layers (*Fig.* 207). Clearly it is possible that a normal duct may be sectioned so obliquely that at the two poles of the obliquity the cells appear to be many layers thick (*Fig.* 208); this appearance must be discounted. Together with this multiplication there is usually a desquamation of the surface layers of cells into the lumen of the duct or alveolus.

FIG. 209.—Desquamated debris. (× 120.)

FIG. 210.—' Colostrum cells '. (× 120.)

Often these cast-off cells disintegrate, and the desquamated products contribute an amorphous debris within the lumen (*Fig.* 209); at other times the desquamating cells appear like colostrum cells with fat globules in their cytoplasm (*Fig.* 210).

Before desquamation the cells of the superficial layer may become tattered or feathery, and the whole process suggests that multiplication of epithelial tissue is outstripping their means of subsistence so that there is an avascular necrosis of the parts farthest removed from the source of blood.

ii. Not infrequently large pale cells make their appearance lining the ducts. These cells, which have a turgid-looking eosinophil cytoplasm, are almost invariably only one layer thick, unless they are thrown into papilliferous projections. They are apparently apocrine in their mode of activity, and it is common to see the peripheral portion of the cytoplasm squeezed off as a secretion into the lumen (*Fig.* 211). I used to regard the appearance of such cells as pathognomonic of the epitheliosis of fibroadenosis, but I have recently observed the change in a fibroadenoma (*Fig.* 212). The origin of these cells has been much debated, but the fact that it is frequently possible to observe, in the wall of a duct, a transition between normal-looking cuboidal cells and these pale eosinophil cells (*Fig.* 213), suggests that they are the result of metaplasia. What

stimulus causes this metaplasia we do not know; nor do we know what the significance of these cells is; certainly there is no evidence that they are pre-malignant.

iii. In contradistinction to these delicate tree-like outgrowths, a more irregular, formidable type of papillomatous projection may be observed. These papillomata (*Fig.* 215) are supported by an abundant

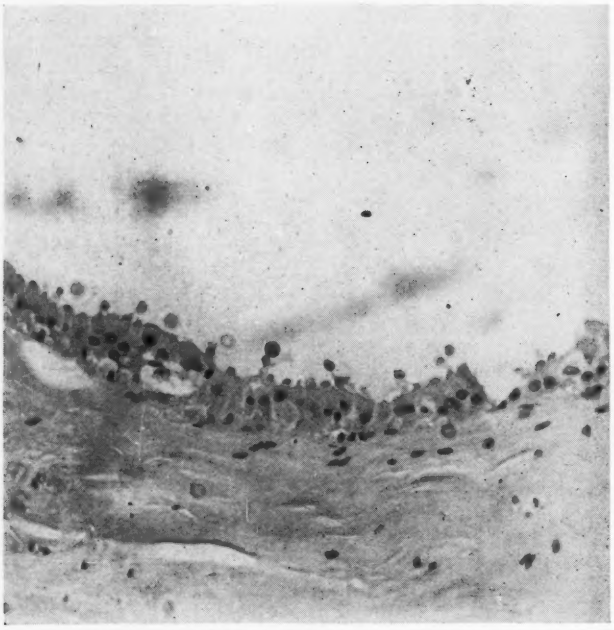

FIG. 211.—Apocrine secretion. (× 250.)

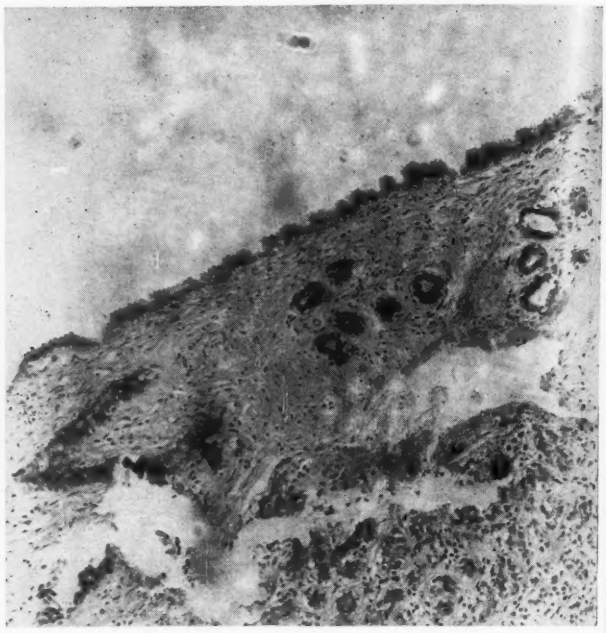

FIG. 212.—Apocrine cells lining a cyst in a fibro-adenoma. (× 120.)

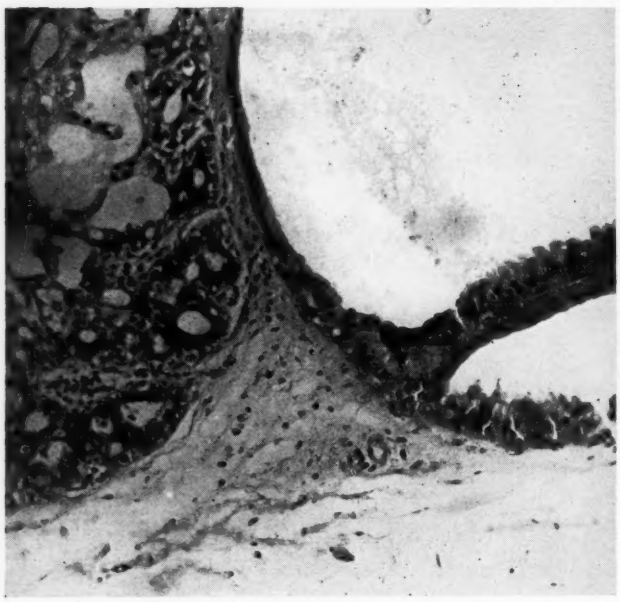

FIG. 213.—Transition between pavement epithelium and apocrine cells lining a cyst. (× 120).

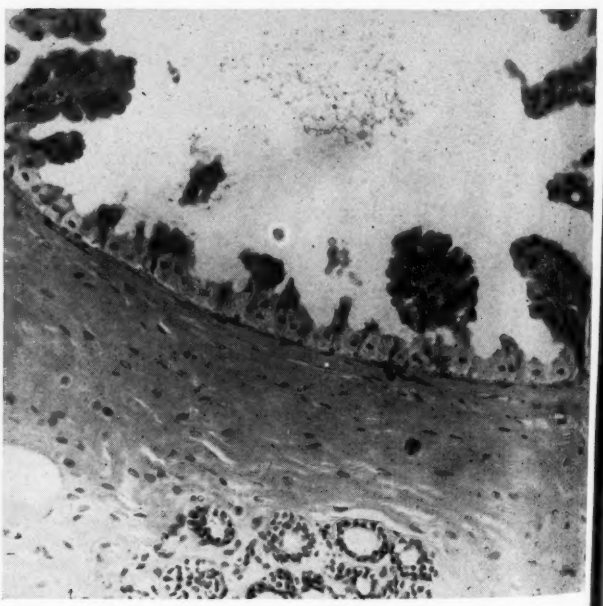

FIG. 214.—Apocrine papillomata. (× 120.)

As we have observed, papillomatous projections of these pale cells commonly occur (*Fig.* 214). These eosinophil papillomata appear fragile and are unlikely to survive if we can judge by the frequency with which, in microscopical section, they appear to fracture at their base, and also by the very poor supporting stroma which they entertain.

stroma carrying well-formed blood-vessels, and the cells lining them are cuboidal, sometimes many layers thick, and contain a normal amount of cytoplasm which shows no particular affinity for eosin.

iv. These papillomata thrusting their way into the lumen of a distended duct may appear to have fused at their tips, giving the appearance of an

arcade or viaduct (*Fig.* 216). Alternatively they may all grow in towards the centre, and this fused appearance makes the lumen of the duct look like the radiating spokes of a cart-wheel (*Fig.* 217).

FIG. 215.—True papillomata. (× 120.)

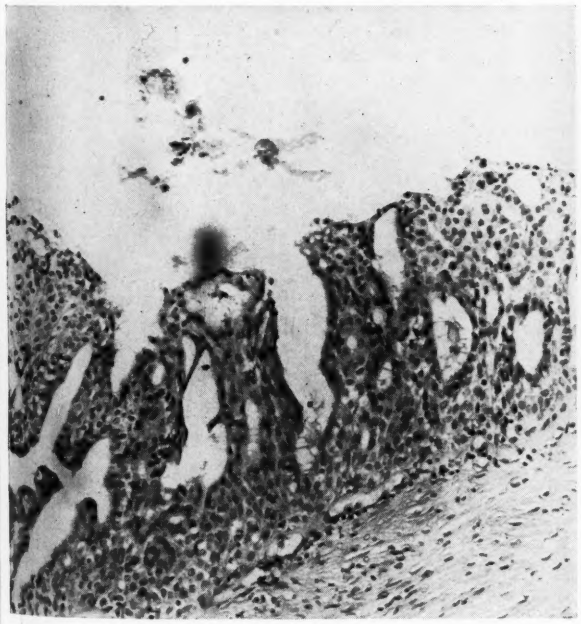

FIG. 216.—Papillomata fusing at their tips to form arcades. (× 120.)

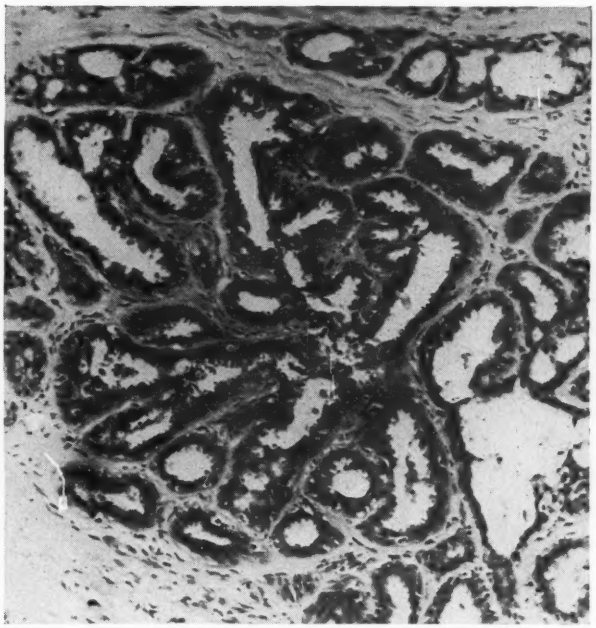

FIG. 217.—Papillomata, growing towards the centre of a cyst, form a cart-wheel pattern. (× 120.)

v. The foregoing processes, if abundant, may reduce the lumen of a duct to veritable chinks (*Fig.* 218).

vi. Epithelial proliferation at this stage constitutes a difficult diagnostic problem for the histologist. Ducts may be crammed with an almost syncytial lamina of epithelial cells, as seen on section (*Fig.* 219), and whether to diagnose such a lesion as malignant or benign depends upon the integrity of the basement membrane, the presence or absence of polarity, the number of mitotic figures, the staining properties of the nucleus, and other morphological characteristics of the constituent cells. It might here be explained that 'malignancy' is a mode of behaviour and not a histological concept. All that the histologist can do is to say that in his experience such an appearance is commonly associated (or unassociated) with malignant behaviour, and the borderline breast section is one of the most difficult problems which he has to solve. Even the most experienced may err, and a section in which all criteria point to innocence (*Fig.* 220) may be taken from a patient who is found to have, in the axillary lymph-nodes, a picture histologically identical with the section from the breast (*Fig.* 221). It is not to be wondered at that the less experienced a histologist is, the more readily will he diagnose a doubtful section as malignant. By so doing a radical mastectomy will be performed and all are safeguarded.

2. Cystic.—We have seen that the epithelial changes described above take place within the lumina of dilated ducts. It is not possible, except by serial secton, and rarely practicable, to determine whether a dilated space seen in section is simply a dilatation of a duct still in continuity with the duct system of that segment of the breast, or whether it is a space shut off from such communication—in other words, a true cyst. It may be that the nature of the epithelium lining this space will determine for us whether such a space is a cyst or a dilated duct, but so far this point has not been successfully investigated. A warrantable hypothesis is that in those spaces where the epithelium is flattened or 'pavement' in type (*Fig.* 222), the system is a closed one, and we are dealing with a true cyst. Where the epithelium is abundant and cuboidal (*Fig.* 223), there is a probability that the duct is still in continuity with the

remainder of the duct system, although exceptions to this latter assumption undoubtedly occur when papillomata or even carcinomata appear in the walls but, with the rise in tension, there is a mechanical restraint put upon epithelial activity, and this latter in time becomes reduced, so that the wall becomes

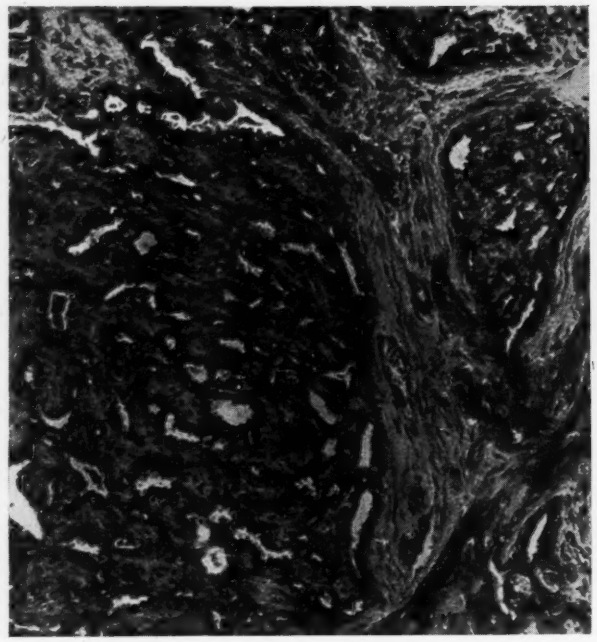

FIG. 218.—The lumen of a duct reduced to chinks in a mass of epitheliosis. (× 120.)

FIG. 219.—Ducts crammed with epithelial cells. (× 120.)

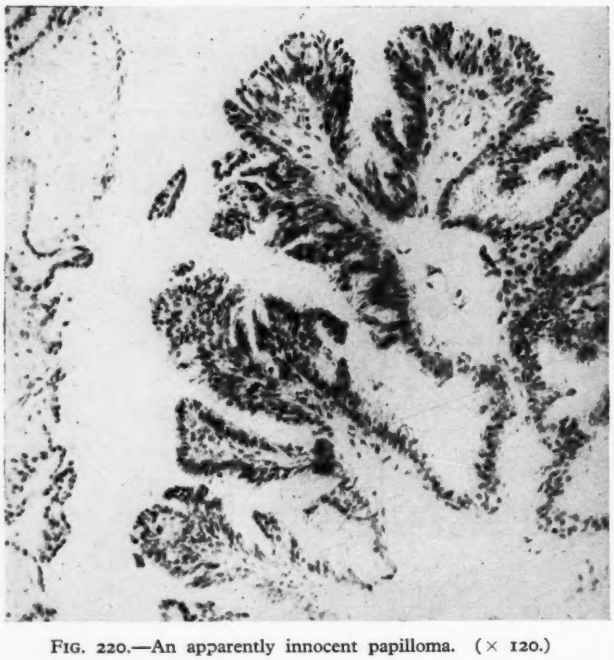

FIG. 220.—An apparently innocent papilloma. (× 120.)

FIG. .221—Section of axillary gland from the same patient as *Fig.* 220, showing epithelial deposits similar to the apparently innocent papilloma in the periphery of the gland. (× 120.)

of unequivocal cysts (*Fig.* 224). As a further primary assumption we may picture the development of a cyst taking place somewhat in this manner. A duct undergoes epitheliosis with desquamation, and dilates. At some stage the outlets from this part of the duct become occluded, possibly by plugging with debris. At first the processes of epitheliosis and desquamation continue into what is now a cyst, a compressed, flattened structure lining an inert cavity in which further epithelial activity is unlikely to occur.

The nature of the contents of cysts and of dilated ducts varies. The consistency may be fluid, creamy, or pultaceous, and the fluid may be clear or turbid.

The colour, if fluid, is pale yellow, deep yellow, yellowish-green, dark olive-green, black, or red; if creamy it is usually white, grey, or green; and if pultaceous, grey or green. The nature of the contents helps to reveal the cellular activity of the tissue from which it derives. An exact histological diagnosis cannot be made from naked-eye study of the contents of a cyst or dilated duct, but a close approximation may be obtained. As a general rule the clearer and more colourless the fluid, the more inert are the cells lining the space in which the fluid lies. Thus the fluid escaping from the puncture of a large 'blue-domed' cyst, lined by flattened pavement epithelium one layer thick, is clear and slightly straw-coloured or colourless. The thicker the contents the more likely is the material to contain the products of cell disintegration, and the 'cheesy', wax-like material which can be squeezed like tooth-paste from the open mouths of dilated ducts which have been cut across, is rich in cholesterol-containing colostrum corpuscles. A study of the significance of the colour of the contents of these spaces is now being carried out, and it will be necessary in this respect to digress for one moment to consider a related aspect of breast pathology, namely, discharges from the nipple.

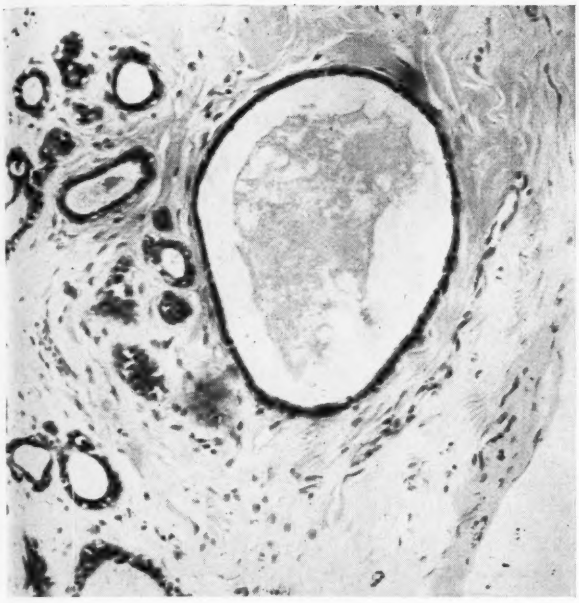

FIG. 222.—Flattened epithelium lining a cyst. (× 120.)

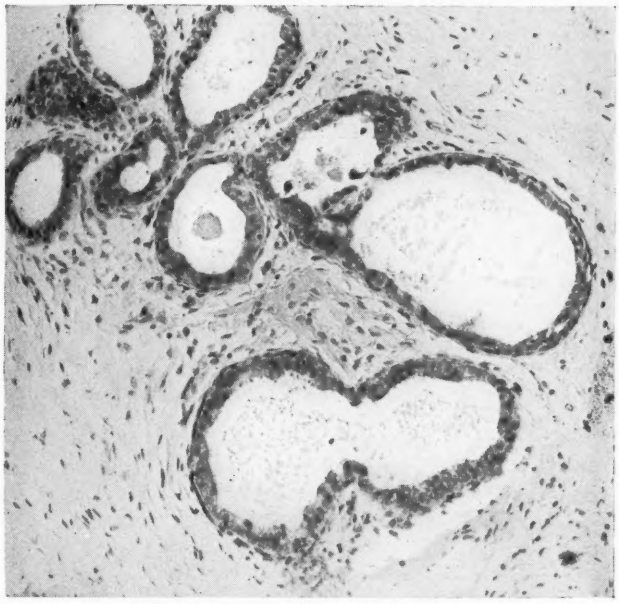

FIG. 223.—Cuboidal epithelium lining dilated ducts. (× 120.)

Histological study has led me to regard as likely the view that the epithelial and cystic changes described above vary in their manifestations, depending upon whether the periphery of the breast is affected or whether the changes are taking place close to the nipple. It is not improbable that where these changes occur in the periphery the escape of the disintegration products of these changes is prevented by the length and tortuosity of the channels connecting this part with the exterior. Somewhere along the duct, and sooner or later, an obstruction occurs, and the processes continue in a closed system so that a cyst results. If, on the other hand, the part of the breast affected is sufficiently close to the nipple, the waste products may not accumulate but discharge themselves, so that a study of discharges from the nipple gives valuable information as to the significance of the nature of the contents of cysts. This study has been undertaken in conjunction with Professor R. H. Thompson, and is not sufficiently advanced to deserve comment except in one particular. Coloured discharges from the nipple, and here we include only green, black, and red discharges, can be divided into two groups: those in which the colour is due to hæmoglobin or its break-down products; and those in which the material is oxidase-negative, and the pigment appears to be melanin. One might

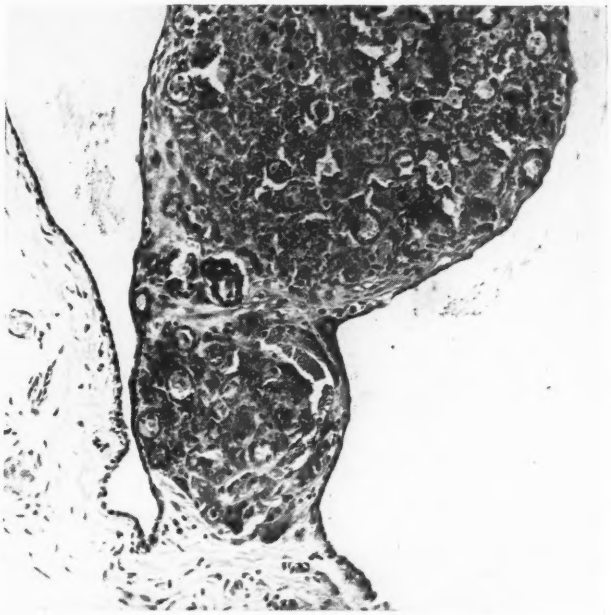

FIG. 224.—A papilloma growing from the wall of a cyst. (× 120.)

incidentally remark that the connexion between œstrogens and melanin pigment is well established in the instance of the pigmentation of the areolæ after œstrogen administration, so that the appearance of melanin pigments in the discharges associated with fibroadenosis is suggestive evidence implicating œstrogens in the changes which occur here.

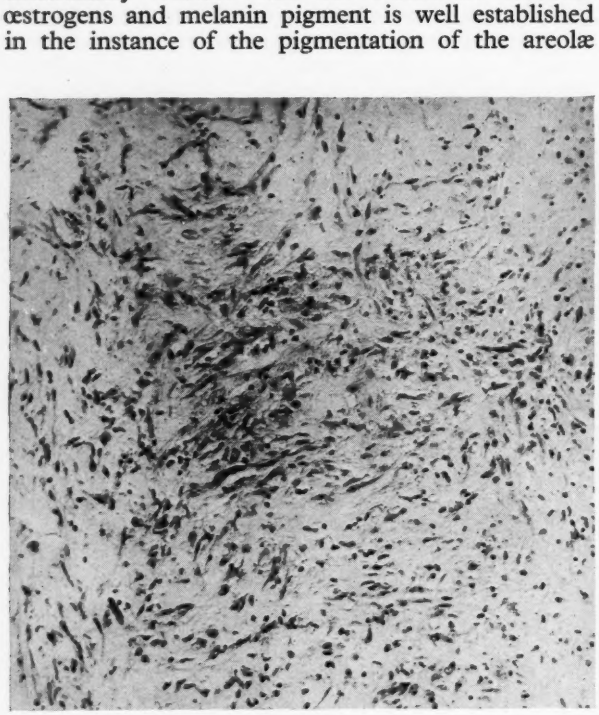

FIG. 225.—Intense fibroblastic activity. (× 120.)

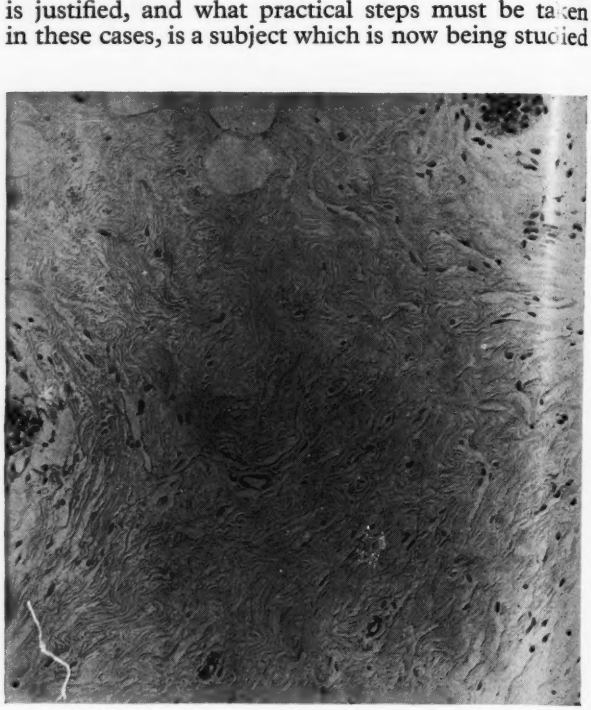

FIG. 226.—Moderate fibroblastic activity. (× 120.)

FIG. 227.—Inert collagen fibrils. (× 120.)

The presence of hæmoglobin or its break-down products either in the discharges from the nipple, in the fluid within a dilated duct, or inside a cyst, indicates a degree of proliferation of epithelium well supported by a vessel-bearing stroma, which is always a source of anxiety. How far this anxiety is justified, and what practical steps must be taken in these cases, is a subject which is now being studied at the Mastitis Clinic, and will be reported on in due course.

The oxidase-negative discharges, on the other hand, certainly have not the *same* significance. This is not necessarily to say that the significance is not equally grave, although our studies so far would indicate that this is not the case, but the histological pattern associated with these discharges is *not* that of an abundant epitheliosis well supported by a vascular stroma.

So far we have considered these fluid accumulations as if they constituted a sort of 'one-way traffic', but there is no doubt that absorption also takes place so that cysts may collapse and, clinically speaking, disappear. It is probable that throughout the life of a cyst there is a balance between accumulation and absorption which is at one time tilted in favour of the former and at another of the latter, a balance which is at least partly influenced by the endocrine changes associated with menstruation and the menopause. There is a third state which also occurs in which both processes have lost their potentials, and a cavity remains stationary, lined with inert flattened epithelium, neither secreting nor absorbing, except at a rate appreciable only over the years.

3. Mesenchymal.—

a. Fibrous Tissue.—Accompanying the above epithelial and cystic changes there is an increase not only in the amount of fibrous tissue, but in its activity. Cheatle and Cutler (1931) have divided the fibrous-tissue stroma of the breast into two types, subepithelial and peri-acinous, and whilst this

distinction is of great importance in the study of the fibroadenomata it is less so in considering fibroadenosis where it is, for practical purposes, only the 'peri-acinous' or, as we should prefer to call it, the 'periductal' fibrous tissue which is involved. The natural history of the stroma of the breast is simple: fibroblasts, plump and vigorous with deeply-staining nuclei, become fibrocytes infused with the lethargy of adults who have attained and passed their prime, eventually deteriorating into inert collagen fibrils, like wraiths haunting the scenes of their former activities.

In fibroadenosis the activity of the fibrous tissue is abnormal only in its excess. Early in the disease fibroblasts are in abundance. A bird's-eye view of the process through the low power of a microscope gives the impression that the stroma has been peppered with deeply-stained nuclei—the nuclei of actively proliferating fibroblasts (*Fig.* 225). Later this appearance is modified, the stromal nuclei become more widely spaced, and their staining properties less (*Fig.* 226). Finally, the field is filled with eosinophil collagen fibrils with here and there an isolated nucleus (*Fig.* 227).

What is the significance of this fibroblastic activity? Some years ago I suggested (Atkins, 1939) that this fibroblastic activity may be protective, and that it prevents uncontrolled epithelial migration, and so accounts for the relative infrequency with which cancer follows fibroadenosis, despite the dangerous-looking epithelial activity which is a feature of this disease. That it is, in fact, like a granulation tissue or abnormality of tissue behaviour due to a carcinogenic factor, as opposed to the granulation tissue which is a response to an infective one. I was advised, by those who understand such things, that this teleological concept was at this stage (and to such a degree) incapable of either proof or disproof, and that the less said about it the better.

The fibrous-tissue reaction has, however, one important significance, and that is that it is responsible for much, if not all, of the pain associated with fibroadenosis. Degrees of pain are almost impossible to assess, and vary so much from patient to patient that the histological pictures associated with different degrees of pain are difficult to correlate. Nevertheless, in general, those patients who complain particularly of pain appear to have an excessive degree of fibroblastic activity in the sections taken for biopsy, and certain it is that when in old age the fires of this disease have burnt low, histological section reveals a mass of inert collagen fibrils.

b. Fat.—Sections of fibroadenosis always show included fat. Bellingham Smith used to remark that this was the only certain way of differentiating fibroadenosis (or chronic mastitis, as he called it) from fibroadenoma. It is true that the latter is nearly always apparently completely encapsulated, but not invariably so. Furthermore, the epithelial changes are usually far less advanced and florid than in fibroadenosis, but again exceptions occur in borderline cases. One may remark indeed that whereas in over 90 per cent of cases the diagnosis as between fibroadenoma and fibroadenosis is clear cut, there is a small proportion in which there is considerable doubt. The presence of a fat globule may be the only indication that the disease is a diffuse process incorporating the *substantia propria* of the breast—a fibroadenosis in fact—and not a localized one which pushes the breast tissue away and excludes it behind a capsular barrier—a fibroadenoma.

The presence of fat is simply this—an indication that these changes are inclusive rather than exclusive. For the same reason nerve-endings proper to the breast tissue are included in fibroadenosis, which is thus usually a painful disease, and excluded from fibroadenoma, which is, by the same token, usually painless.

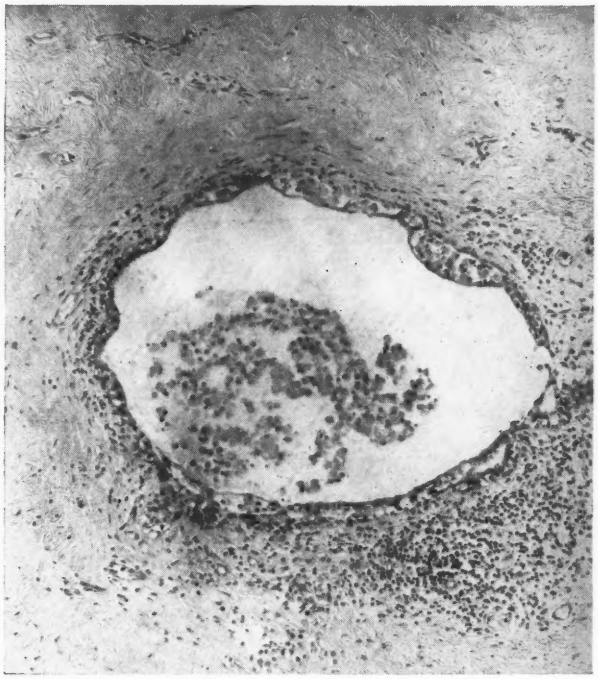

FIG. 228.—Post-mortem section showing cyst containing colostrum cells. (× 120.)

c. Lastly, there is a small round-celled infiltration, especially of the periductal fibrous tissue. This infiltration is particularly marked, as in the normal breast where it occurs to a slight extent, before the menstrual period, and it is probably allied to the swelling of the regional lymph-nodes which occurs at these times. Its significance is bound up with the problem of lymphocytic function throughout the body, a problem which has not yet been solved.

Such, then, are the histological changes encountered in the breasts of women complaining of fibroadenosis; but are these changes exclusive to such women? *Figs.* 228–230 are sections taken at the post-mortem table from the breasts of women not known to have made any complaint about their breasts during life. It will be seen that many of the changes described above can be found in such sections, and we must therefore conclude that fibroadenosis, a disease, as we have seen, without a 'beginning point' clinically, is histologically in the same case. The late Professor Rutherford Morison (1916), in a paper read to the Northumberland and Durham Medical Society in 1911, remarked, "If

a portion of the healthy breast of a woman near the menopause is examined by a pathologist, his report on it is invariably ' interstitial mastitis ' ".

If, then, the outlines of the disease fibroadenosis appear so hazy both clinically and histologically, what can we say of such a ' will-o'-the-wisp ' ? A parallel suggests itself from the world of physics in which the ' Principle of Indeterminancy ' has to be accepted.

FIG. 229.—Post-mortem section showing papillomata growing into cysts. (× 120.)

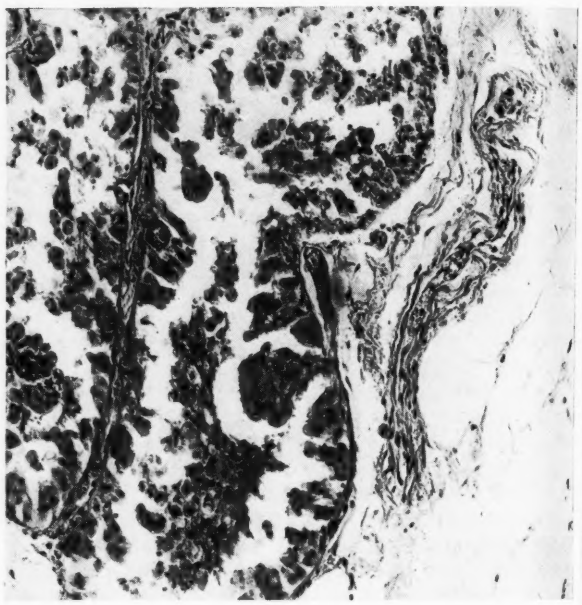

FIG. 230.—Post-mortem section showing apocrine papillomata in cysts. (× 120.)

The more meticulous, the more precise is the endeavour to measure the nucleus of an atom the more elusive it becomes, and like the rainbow's end, can never be grasped and analysed. So it is with fibroadenosis. That the disease exists as an entity there can be no denial, but at what stage it becomes a disease no one can say.

NATURAL HISTORY AND PHYSICAL SIGNS

Age Incidence.—Fibroadenosis is met with in a specialized form in infancy, to a less extent throughout childhood, at puberty, and during adult life. It is not proposed to discuss these types as they differ in material respects from the common fibroadenosis of later life. Histologically the changes are almost exclusively of minimal degree and their natural resolution may be anticipated. Further, their appearance does not presage disease subsequently.

Fig. 231 illustrates the age of onset in the cases coming up to the Mastitis Clinic. It will be seen that the commonest period for the disease to manifest itself is between the ages of 20 and 50.

Sex.—The vast majority of cases are seen in women, but fibroadenosis before puberty has a more equal sex distribution. Cases in men during later years are characterized by a firm painful plaque of tissue, often subareolar in situation, which persists for many months or even years. Its tendency to malignant transformation is minimal, and there is some evidence that its course may be shortened by the prescription of androgens. Occasionally excision may be called for because of the annoyance of a persistent, painful lump.

Symptoms.—Pain, the presence of a tender lump or lumpiness, or the discovery of an area of thickening, all of which are accompanied by anxiety, are the reasons for patients consulting their doctors.

Discharges may appear from the nipple, the significance of which has been discussed above.

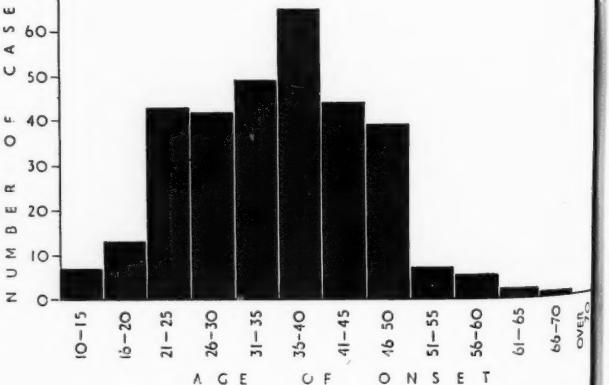

FIG. 231.

The pain is not severe, but the natural fear that the lump may be a cancer aggravates this symptom so that a sensation becomes a pain, and a pain an agony. There is often both a long- and short-term periodicity to this pain. The long-term periodicity is expressed as intervals of freedom lasting over months or years, interspersed with painful periods

lasting as long. On to these active periods the short-term periodicity is grafted. From ten to seven days before menstruation until the first or second day of the menstrual period the pain is often exacerbated. Many patients are so regularly afflicted in this way that they volunteer the information spontaneously, others admit to a premenstrual exacerbation on questioning, but in a few there appears to be no relation between the menstrual process and the severity of the symptoms.

The other symptoms, namely, the presence of a tender lump or of a thickened area, often vary in the same way in relation to the menstrual periods. The increase in symptoms at these times is no doubt partly accounted for by the increased vascularity of the breast in the premenstrual period, but there may be in addition a specific endocrine effect causing an epithelial and fibrous tissue proliferation at these times.

Signs.—The lumpiness which is characteristic of the disease may be diffuse throughout both breasts, diffuse throughout one breast, aggregated into a quadrant of one or both breasts, or be so circumscribed as to constitute a lump.

Before discussing the individual qualities of the lumpiness it will be necessary first of all to describe the physical signs of a lump of fibroadenosis, so that a tentative diagnosis may be made from other conditions, such as cancer and fibroadenoma, which also cause lumps in the breast. I say ' tentative diagnosis ' because where fibroadenosis is so circumscribed as to cause a lump, the diagnosis is never certain until the tissue has been examined under a microscope. However that may be, there are qualities of such a lump that are indications of much value.

At first, the lump may be nothing more nor less than a cyst, or this cyst may be surrounded by an area of fibroadenosis in which cystic changes do not predominate. A cyst of the breast, like cysts elsewhere, fluctuates, and few cysts are so tense that with care and trouble they will not vouchsafe this sign. This is not to say that all fluctuant breast lumps are cysts, because a soft cancer will also appear to fluctuate and so may a sarcoma or a lipoma, but a smooth-surfaced lump, free from tenderness and present for years, which fluctuates, is virtually certainly a cyst.

Other solitary lumps are due to segments of breast tissue exhibiting the changes of fibroadenosis in advance of adjacent areas, or exhibiting them exclusively. The qualities of such a lump are so well known and universally taught that it is only the excuse of making this account complete that saves their recital from impertinence. The lump is often sector-shaped, and it may be tender, the edge is usually ill-defined, but not invariably so, particularly where a plaque of granularity which has been present for a long time can be felt immediately beneath the skin often in the tail of the breast. The lump is felt better between the fingers and thumb than with the flat of the hand. There is only exceptionally tethering to the skin or nipple, and deep attachment cannot be demonstrated. The consistency is firm, but not hard, and the surface, like the surface of the breast when the condition is diffuse, is spread throughout the organ, is granular, nodular or lobular.

Granularity.—This quality is defined above as the state of breast tissue in which the discrete nodules are a millimetre or two in diameter, and feel like pins' heads. It is a condition of great interest, and biopsy material taken from an area of granularity shows usually a simple adenosis, each little granule being a clump of alveoli which stands out firmly from the surrounding fat and loose areolar fibrous tissue.

Multiple small cysts only very occasionally give rise to granularity. After all, the surface of the breast felt by the flat of the hand through the skin is really part of the periphery of the breast looked at from the physiological point of view. The subcutaneous surface is therefore occupied by alveoli, which do not become cystic, the ducts lying more deeply by some millimetres. These latter, which are the source of the cysts, have to enlarge to the size of half a centimetre before they become appreciable through the skin, and nodules of such a size do not give the impression of granularity.

Nodularity.—This feeling is given by discrete masses of a half to one centimetre in diameter, and the lumps are usually small cysts or nodes of fibrous tissue separating areas of epitheliosis. Occasionally small nodules of fat popping through the interstices of a fibrous framework will give the impression of nodularity.

Lobularity.—When the lumps to be felt are over a centimetre in diameter, we apply the term ' lobularity ' to the change. The lobules are often more or less uniform in size, in which case they are usually lobules of fat, but the condition of fibroadenomatosis (multiple fibroadenomata) also gives this feeling, and this condition is usually distinguished by the painless nature of the lobules and the younger age of the patient. The lobules themselves are firmer in consistency than when due to fat.

Multiple cherry-like cysts may occasionally give rise to lobularity, but the lobules are rarely uniform either in size or distribution, and fluctuation in the larger of these will reveal the diagnosis.

Natural History.—Coming on in the early thirties, fibroadenosis pursues a checkered career for many years. At times it is a cause of distress and the physical signs are prominent, then for weeks, months, or years the disease will be quiescent. Eventually, at or about the menopause, the pain disappears, and the lumpiness becomes less obvious. Such is the usual course, but exceptionally the pain may persist, one is tempted to assume, as a neurosis. Exceptionally, too, a lump, due to a large cyst, lingers on for many years when all other evidence of the disease has vanished.

The effect of pregnancy on the disease is of some importance. First, the disease is rare in patients who have borne many children. The accompanying diagram (*Fig.* 232) shows the fecundity rate of patients attending the Mastitis Clinic, and it will be seen that very few are mothers of large families.

Secondly, in those patients who already have the disease, pregnancy usually exerts a beneficial effect. Fourteen patients attending the Clinic have become pregnant, and in many of these the symptoms disappeared during the later months of pregnancy for a period of months or years.

The common experience is that both symptoms and signs disappear during the later months of pregnancy, and remain in abeyance thereafter for some eighteen months to two years.

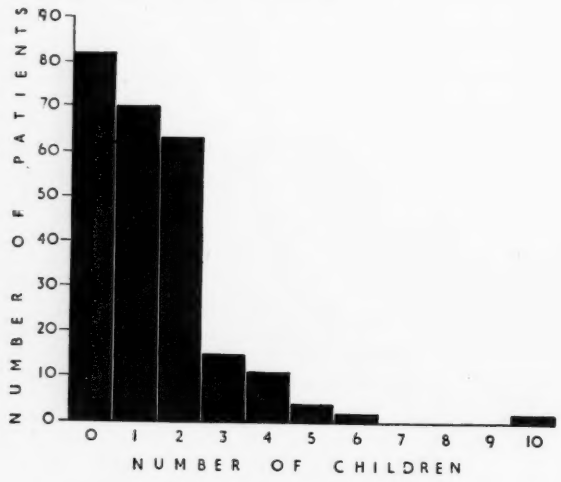

FIG. 232.—Fecundity rate in fibroadenosis.

Aetiology.—Having confined ourselves so far, and for the most part, to ascertainable fact, we may perhaps be allowed to indulge for a short while in the dangerous delights of speculation. For speculation it undoubtedly is. We do not know what is the cause of fibroadenosis, and recent work, far from clarifying the issue has, if anything, made it more complicated—and fascinating.

It will not be possible in this short review to refer in detail to the mass of experimental work which has been undertaken in an attempt to clear up this and allied problems. Most of the important studies have concerned themselves with the effects of endocrines upon breast tissue. By the prescription of œstrogens to certain mammals changes can be produced in the breast microscopically similar to, but by no means identical with, those met with in fibroadenosis in the human (*Fig.* 233). By the prescription of œstrogen preparations similar histological changes may be produced in the human breast, and, lastly, by prescribing œstrogens in effective doses to patients suffering from fibroadenosis, the symptoms are usually aggravated, and the microscopical picture worsened (*Figs.* 234, 235).

Such evidence tempts one to characterize fibroadenosis as an œstrogen-stimulated disease, but the more the effect of œstrogens upon breast tissue is studied the less satisfactory does this simple explanation appear. This is not to suggest that œstrogens (or other endocrines) may not play a significant part, but that that part is not the whole story. If it were, the disease could be precisely reproduced by the prescription of œstrogens, and this is not so. Œstrogens stimulate an epithelial proliferation which may even, as we shall see, proceed to cancer, both in the experimental animal and in man; but this picture differs from that of fibroadenosis in material respects, the most important of which is, perhaps, the absence of excessive fibrosis. Again, œstrogens do not always stimulate epithelial activity in breast tissue if these epithelial cells have become neoplastic, as witness the regression of certain cases of cancer of the breast under the influence of œstrogen therapy. Finally, androgens, assumed to exert an opposite effect to œstrogens on breast tissue, may in fact stimulate epithelial activity in a way almost indistinguishable from the effects of œstrogens.

These considerations make one wonder whether the effect may not be an indirect one, taking place through the intermediary of some other organ of internal secretion such as the pituitary or the suprarenal cortex. Alternatively the endocrine imbalance may be one shared by a number of organs, in some cases one preponderating, in some cases, others.

That endocrines, and particularly œstrogens, are implicated, however, receives sanction from clinical considerations. Thus the symptoms and signs of fibroadenosis vary suggestively with the chapters in the endocrine history of the patient: puberty, menstruation, pregnancy, and the menopause.

I have a suspicion that in this, as in so many other diseases, tissue response may be as important as stimulus; that there may, in fact, be an inherent and possibly inherited quality of the breast tissue which determines the nature of the response to hormonal stimuli. Without labouring a point to which tentative reference has already been made, we may consider the possibility that fibroadenosis

FIG. 233.—Section of breast of a Dobrovolskaia-Zavadskaia male mouse painted with 0·01 per cent œstrin for 6½ months. Note relative absence of fibrosis. (× 120.)

is an expression of a particular response on the part of the patient to growth-stimulating factors.

A further and probably important consideration is the age at which the stimulus becomes effective, and perhaps the duration. It is a hypothesis worth while considering that the same stimulus acting upon the young may produce one sort of effect—a fibroadenoma; on the somewhat older a different effect—a fibroadenosis; and on the middle-aged or elderly yet a third—a cancer.

To make comprehensive the possible fields for speculation we must consider how a virus, if virus there be, in the causation of breast cancer might fit into this picture. Modern views on the aetiology of breast cancer suggest that three factors may be necessary, a virus, a hormonal factor, and a genetic factor. Recent work has shown that breast cancer in mice may be due to a virus normally passed in the mother's milk. This agent, however, only produces its characteristic lesion in a breast that has been adequately stimulated by a second factor, namely, a hormone. Thirdly, the genetic constitution of

FIG. 234.—Random sample of breast in woman aged 34 complaining of the symptoms of fibroadenosis. (× 120.)

the animal plays an important part in deciding the outcome. The genetic basis is complex, and mice do not fall sharply into susceptible and resistant groups. If these three factors operate in the production of cancer of the breast in mice it is reasonable to investigate the possibility of a similar mechanism in man, and if such a mechanism exists, is it possible that fibroadenosis is the response of the patient to two of these factors in the absence of the third? It might be argued that if this were so cancer of the breast could not follow fibroadenosis as it undoubtedly occasionally does—a point which will be considered fully in the next section. For, if a patient with fibroadenosis has not the genetic factor this cannot be superadded; if the virus is conveyed in the maternal milk this, too, cannot be superadded: and we have already postulated a hormonal effect for fibroadenosis, so that the superaddition of this factor is not necessary. However, the matter is not so simple. The genetic factor may not be of the 'all or none' type, and a patient whose natural tendency is to respond by fibroadenosis to the impact of the other two factors may have that tendency overwhelmed and submerged by an excessive application of the one or the other. Such a possibility is suggested by the fact that provided sufficient œstrogen is administered to many experimental animals and even perhaps to man, cancer of the breast can be produced whatever the innate immunity from the disease. Furthermore, although there may be a virus specifically associated with cancer of the breast and possibly conveyed in the maternal milk, this virus need not be the only possible virus agent and other viruses acquired at a different age or in different ways may occasionally function carcinogenetically.

Such considerations do little other than stimulate further inquiry. It would seem that the most

FIG. 235.—Random sample from an area adjacent to that depicted in *Fig.* 234 after the administration of 100,000 units œstradiol benzoate. (× 120.)

important point to be determined is the existence or otherwise of a virus in the genesis of human breast cancer, and if it exists the nature of this virus and how it is transmitted. Such an investigation may consume many years, or may suddenly and unexpectedly yield results. At least the machinery for its prosecution is ready to hand.

The Precancerous Nature of Fibroadenosis.—The foregoing considerations have carried us very close to the problem of the precancerous nature of fibroadenosis. The evidence that fibroadenosis is precancerous is experimental, histological, and indirect.

We mentioned above that the injection of œstrogens into certain experimental animals determines the appearance of cancer of the breast where it would otherwise not have appeared. Furthermore, these injections stimulated first of all changes similar to those of fibroadenosis, which later became neoplastic, suggesting that fibroadenosis is a halfway house on the way to the formation of cancer. The fallacy in this argument (although a fallacy in an argument does not necessarily invalidate the conclusion, which may be correct for other reasons) is to assume that the intermediate stage is what it superficially resembles, namely, a fibroadenosis. There must be

considerable doubt about this matter, especially in view of the relative feebleness of the fibrous tissue reaction in such artificially stimulated hyperplasias in comparison with the marked fibrous tissue reaction in the naturally occurring fibroadenosis in man. As we have hinted—this fibrous tissue reaction may be protective.

Histologically the game of arranging a number of microscopic slides in a series showing a normal breast at one end of the scale, all the intermediate phases of fibroadenosis in the middle, and cancer at the other, is one which few histologists can resist playing. This game can be played by regarding *Figs.* 207 and *Figs.* 215–219 as a sequence. That the evidence which such a series presents demands the most serious consideration is obvious; it is at least as suggestive as much of the evidence quoted above in support of other hypotheses. Nevertheless, like all hypotheses it must stand up to bombardment because it does not logically demand assent. To apply to it the healthy rule of *reductio ad absurdum*, it might, for instance, be cited equally to show that the normal breast develops from carcinoma through all the stages of fibroadenosis in the reverse order. Let us not, however, be betrayed by the attractions of smart retorts which smother truths. If we walk along a street and pass a group of men working on the foundations of a wall two bricks high, later we meet one six bricks high, and finally encounter a gang of plasterers putting the finishing touches to a wall thirty bricks high, we are entitled to assume that, *unless anything prevents it* the first wall will eventually become like the last through the intermediary of the second.

One of the fallacies in the histological argument for the precancerous nature of fibroadenosis, and perhaps the most important, is that it does not take into account the striking fibrous-tissue reaction which accompanies the epithelial changes, and which has no part in the stimulation of cancer and may indeed be inimical to it. To return to our metaphor —our anticipation of the completed wall takes no account of strikes and industrial disputes which may put a stranglehold upon building and so prevent its realization, and which may be inseparable from these particular conditions of working. Such strife may be more the essence of the disease than the building.

Let us relinquish, therefore, the uncertain paths of indirect evidence and inquire whether cancer does indeed follow fibroadenosis in a higher proportion of cases than in the normal population. What a simple proposition, and what a disappointment greets us when we proceed to examine it! The path of direct evidence leads us directly into the wood.

We have heard, as the result of a most valuable and painstaking piece of statistical research by Warren (1940), that cancer is 4·5 times as common in patients with chronic mastitis as in the normal population. But which, we may pertinently inquire, are the patients with ' chronic mastitis ' and which ' normal' ? We have seen that fibroadenosis is a disease clinically and histologically without a ' beginning point '. The boundaries of this entity are so indistinct that it is misleading to attempt to reduce to figures frequencies which cannot be so expressed. To take such figures to the second place of decimals, as has been done, is to bask in the penumbra of pseudo-scientific artificial light, which requires a shaft of sunshine and a breath of fresh air to reveal its insubstantial and tawdry character.

" Is fibroadenosis a precancerous lesion ? " is a question which has not been answered because it is not yet a question which may properly be put. To ask such a question it is necessary to define, or to be able to define, with a degree of precision as yet unattainable, the terms used. Much of the burden of the thesis of this paper has been to show that, with our present methods of investigation, we are not able to define, or at least have not yet defined, fibroadenosis sufficiently precisely for such a question to have a precise meaning. It may be that we never shall be able to do so. What concerns us far more nearly as practising surgeons is what advice we are to give to a patient coming to us complaining of a painful nodular breast; and figures, provided that they are manipulated with understanding, will help us to decide. Since 1936, 326 patients have attended the Mastitis Clinic complaining of fibroadenosis. Because of the interruption of the war only 255 have been followed up, and two of these have developed cancer during the last fourteen years. Upon these and parallel figures by Bloodgood, Warren, and others, we may plan our treatment.

TREATMENT

When the diagnosis is assured the treatment of fibroadenosis is reassurance and regular inspection.

The diagnosis of fibroadenosis can frequently be made unequivocally on account of the diffuse nature of the lesion and a combination of qualities all pointing in the same direction.

This being so, there are various measures which have from time to time been adopted, but for success reassurance must accompany them, and it is my belief that reassurance is the chief therapeutic agent in the recipe. That we are justified in reassuring the patient there can, from a consideration of the figures quoted above, be little doubt. The chances of cancer appearing in the breast in a patient suffering from fibroadenosis is, as we have seen, sufficiently small to be ignored. There is certainly no excuse for removing the breast of such a patient in order to prevent cancer, and it will be sufficient to examine the part from time to time. It may be propounded that such an attitude is an admission that fibroadenosis may be a precursor of cancer and is an illogical consequence of the reassurance which has been given, and so it is. But if we must eschew illogicality in our thought we may be permitted to compromise in our treatment of patients where logic must be tempered by judgement; where other considerations such as the psychological and physiological aspects of the case, together with expediency, must be taken into account. Fortunately fibroadenosis is a disease of women, who wisely abandon logic in human relations, and only one out of 326 has said to me: " but if there is nothing to worry about, why do you want to see me again ? " In practice most women are overwhelmed with relief at hearing that they have not got cancer, delighted to hear that their chances of getting cancer are negligible, and grateful for the opportunity of unloading any further worry in this respect on to the shoulders of

their medical attendant, who they are assured will wish to examine them at regular intervals of about six months.

The alternatives to such a course are either to tell the patient that they may have an increased liability to cancer because of this disease, intelligence which will render their lives intolerable from anxiety and worry, and worsen every aspect of their present disablement, or to remove one or both breasts, a course which in the last fourteen years would have led me to perform over 600 mastectomies unnecessarily, and one which as a practical surgeon I would not entertain for one instant.

The effect, on the other hand, of the first course is very gratifying. The symptoms which have been magnified by natural anxiety become scarcely noticeable, and the patient treats her premenstrual discomfort or pain with the same disdain that she would accord to slight dysmenorrhœa, knowing that it has much the same significance.

What of the patient who does not respond to this therapy, who continues to have 'agonizing' pain despite all reassurance? My experience of such patients has been of the greatest interest. Many of them turn out to be errors in diagnosis. Intercostal neuralgia, spinal arthritis, cardiac pain, and cholecystitis have been unearthed as the cause of the 'mammary' pain in the Mastitis Clinic. Nevertheless, there is a residue of patients whose pain undoubtedly started in disease of the breast, but which no therapy will touch.

It is no use removing the breast in such cases. Between 1936 and 1938 I performed bilateral mastectomy upon 6 such cases after "everything else had been tried". Four of these patients still complain of intolerable pain where the breasts were, and the remaining 2 have transferred their 'agony' to other sites. One of these two could not be traced after the war, but on going round my patients in the wards of Guy's Hospital recently, my house surgeon took me to a case with the symptoms of gall-stone colic. "You will be interested in this case", he said, "because in 1938 you took both her breasts off for fibroadenosis". The lady, now aged 47, was a hospital nurse, and I asked her how the 'breast trouble' had been since the operation. She assured me that she had been quite free from symptoms in this respect, and I had to point out to my firm that this was the first case that I had encountered in which such an operation had been successful. I then proceeded to examine her, and elicited a history of gall-stone colic, each attack being accompanied by "a tinge of jaundice". The gall-bladder area was exquisitely tender and Murphy's sign was positive. Cholecystogram was normal, but the clinical picture was so perfect that I arranged to operate. Two days later I removed a gall-bladder, normal in every respect!

I would not publicly acknowledge the folly of having been—'seduced' I think is the proper term—twice by the same patient into performing mutilating operations on account of the importunities of a deranged mind, unless the experience had taught me an important lesson. It is my firm conviction that apart from bacterial inflammation, and the excessive inroads of an advanced cancer, no disease of the breast is so painful that the patient cannot make the best of it; and if the pain is of an "agonizing" or uncontrollable quality its origin is not in the mammary organ, but in some remote region of the central nervous system, the very whereabouts of which is beyond the comprehension of the operating surgeon.

From time to time patients in the Mastitis Clinic have been given X-ray therapy, and another series radiant heat. The former method of treatment has, in my experience, been disappointing, and the latter only very temporarily effective.

The main mass of the work in the Clinic has been devoted to the investigation of the effects of various endocrine preparations in this and other breast diseases. A full account of the findings has been published (Atkins, 1949), and it will suffice here to reiterate the general conclusion. "In a substantial proportion of cases androgen therapy causes temporary improvement in the symptoms of fibroadenosis. The safest, most effective, and most convenient way of administering androgens is in doses of 15 mg. of methyl testosterone by mouth daily for two months. Androgen therapy has less, if any, effect upon the nodularity, and no constant detectable effect on the histological picture. My view is, nevertheless, that androgen therapy is not worth while in fibroadenosis. The pain, divorced from the apprehension, is rarely excessive, and the vast majority of patients, relieved justifiably of their apprehension, forget it."

We come now to the case where fibroadenosis is expressed in a form so localized as to constitute 'a lump', and in which *inevitably*, therefore, the diagnosis is uncertain. Such cases are all operated upon, and the lump is removed together with an area of surrounding tissue. While an assistant fills the cavity with gauze and applies pressure, the lump is thoroughly examined by the naked eye, section being made in many planes, and the cut section examined in a good light, carefully palpated, and scraped with a knife. In all but a few such cases a diagnosis can be made confidently upon such a specimen, but there are a few in which doubt still prevails, and all lumps are subjected to expert frozen section.

The value of frozen sections, expertly performed, is incontrovertible. Fat necrosis and pyogenic inflammation can be diagnosed with little difficulty, but there is furthermore an appearance of the gross specimen, which it is impossible to analyse by naked-eye inspection, but which frozen section will resolve with certainty. I refer to the grey-white surface speckled with greyish-yellow dots about the size of a pin's head. Such an appearance is given by certain types of adenosis, by some intraduct papillomata, and by certain cases of comedo cancer. The resolution of these different states by microscopical examination of the frozen section is revealed in *Figs.* 236–238.

Expert naked-eye inspection is far more certain than inexpert frozen section, but where the techniques of both have been mastered their combination is the surest guarantee against error. If examination has established the lesion to be one of fibroadenosis, I believe that the proper course is to obliterate the dead space, formed by the excision of the lump, by means of fine sutures threaded on a trocar-pointed

needle, to drain the deep part of the wound by a narrow piece of corrugated rubber inserted through a stab wound at the side of the breast or in the submammary groove, and to stitch up the skin, a firm binder being placed over the dressing.

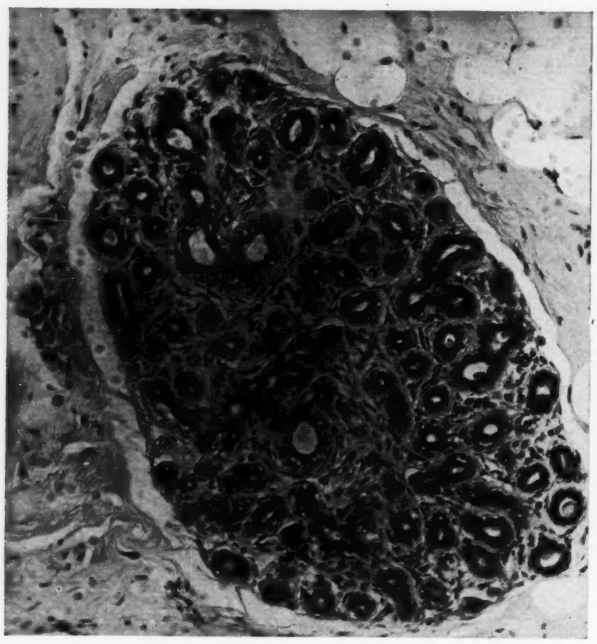

FIG. 236.—The grey-yellow dot is revealed by the microscope as an area of adenosis. (× 120.)

FIG. 237.—The grey-yellow dot is revealed as a papilloma within a cyst. (× 120.)

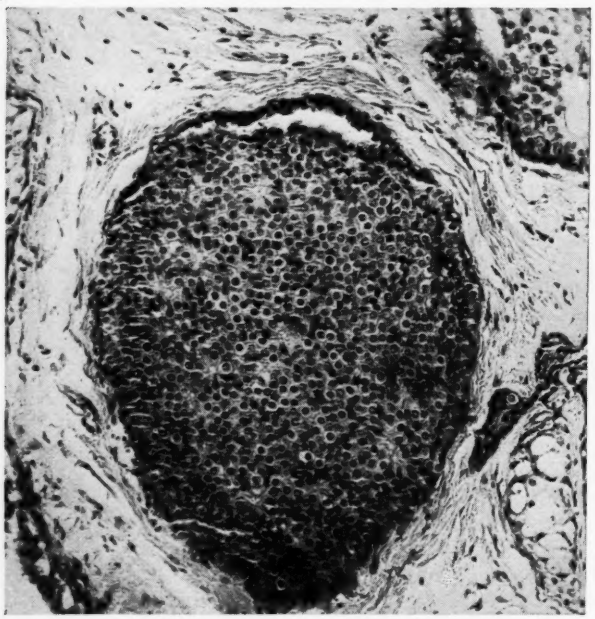

FIG. 238.—The grey-yellow dot is a duct containing cancer cells, and such a patient should have a radical mastectomy performed. (× 120.)

There are those who say that such a procedure will lead to recurrence, and that fibroadenosis is a disease of the whole breast, so that, in these circumstances, mastectomy should be performed. But this is surely neither logical nor sensible. To be logical both breasts should be removed because fibroadenosis is a disease of the whole of both breasts; it is not, furthermore, sensible to remove the whole breast from a woman who may get no further trouble by being left alone. The crux of the matter is this —how often do lumps reappear and a second operation become necessary in the breast of a woman who has had one lump of fibroadenosis removed? The figures are not yet available for study, but early impressions (notoriously fallacious) lead one to suppose that at least two-thirds, and it may be a much higher proportion, of women who have had one lump of fibroadenosis removed do not again require further operation. And even if they do, is such a fate so awful to contemplate? The first operation has, so far as the patient is concerned, proceeded so unexpectedly smoothly and painlessly that there is rarely any difficulty in persuading her to undergo it again. She is the first to admit that while an edentulous patient never has toothache, that is no excuse for universal extraction.

Here, then, in fibroadenosis we have a disease which, despite intensive study for two hundred years, still presents problems for solution. Many of these problems concern the fundamental processes of growth, overgrowth, and restraint, so that in their solution, if they be ever solved, findings of supreme biological importance may emerge. These processes take place in an organ superficially situated, and susceptible to minute clinical examination. The breast, in fact, is like a laboratory with frosted-glass windows in which most of the biological processes of nature occur with tantalizing semi-obscurity. It is an organ of simple fundamental structure, controlled by nervous and hormonal influences which can be observed; susceptible to bacterial inflammation, new growth, and involution, processes which serve as a pattern for similar behaviour in organs

more remote. Its study is both simple and complex, its behaviour obvious and obscure; within it may lie the solution to the problems of new growth.

SUMMARY

1. The work of the ' Mastitis Clinic ' is described. It is pointed out how difficult it may be on clinical grounds to draw a hard-and-fast line between the patient with a ' normal ' breast and a patient suffering from fibroadenosis.

2. The histological changes occurring in fibroadenosis are discussed with a short note on the significance of pigmented discharges from the nipple. It is observed that similar histological changes are often found in random samples taken from the post-mortem room. It is shown how, in this disease, it is histologically almost as difficult as it is clinically to distinguish precisely between the normal and the pathological. Fibroadenosis, both histologically and clinically, has no ' beginning point '.

3. An account is given of the natural history and physical signs of fibroadenosis, and some views regarding the aetiology of this condition are examined.

4. The possible precancerous nature of fibroadenosis is discussed. Since this is a disease without a ' beginning point ', and as it is therefore impossible in many cases to say, " This breast is normal and that is pathological ", this cancerous tendency (if it exists) cannot be expressed in terms of figures. Experience has shown that, with our present knowledge, no specific action need be taken in patients suffering from fibroadenosis to prevent the onset of cancer of the breast.

5. The treatment of fibroadenosis consists in making an accurate diagnosis followed by reassurance. The patient should subsequently be examined periodically.

I should like to thank Sir Heneage Ogilvie, Dr. S. J. de Navasquez, and Dr. P. A. Gorer for reading through this paper, and for their helpful suggestions. I am indebted to Professor A. Haddow for *Fig.* 233, showing the effect of œstrogens on the breast of a mouse; and to Mr. J. F. Dudley and Mr. E. W. Meyer for the great trouble they have taken preparing the photomicrographs.

All expenses incurred at the Mastitis Clinic are covered by a grant from the British Empire Cancer Campaign.

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INFLAMMATORY CARCINOMA OF THE BREAST*

A REPORT OF 20 CASES AND A REVIEW OF THE LITERATURE

BY S. MILTON CHRIS, LONDON

THE recent admission to the surgical wards of Hammersmith Hospital, within a short space of time, of two patients with advanced mammary carcinoma showing the unusual appearance of widespread redness and œdema of the skin due to neoplastic infiltration (the so-called ' inflammatory ' carcinoma of the breast), led to a search of our hospital records for similar examples of this condition, and as a result a further 18 cases, making a total of 20, were found to have been admitted to our wards in the 3-year period June, 1946, to May, 1949.

The purpose of this paper is to present these 20 cases and to correlate the findings in them with those of the 220 cases previously recorded in the literature.

Inflammatory carcinoma of the breast has become recognized as a distinct variety of mammary cancer possessing certain characteristic clinical and pathological features; it is of great interest to the surgeon by reason of the errors not infrequently made in its diagnosis, the rapidity of its spread at an early stage, and the consequent grave prognosis of the disease. The cases in this series have been selected on the basis of the presence of a definite cutaneous redness and œdema associated with a carcinoma of the breast, and care has been taken to exclude those cases of mammary cancer in which a local skin redness was attributable to pyogenic infection of an ulcerated growth and those in which the erythema of the skin was the result of irradiation.

Of the 20 cases in this series, I have personally examined 9 at varying times within the last year; the remaining 11 have been included after careful study of their descriptions in the hospital case records.

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HISTORICAL

The condition of redness in the skin overlying a cancer of the breast was first described in 1814 by Charles Bell, who commented upon the grave prognosis in these cases, writing that " when a purple colour is on the skin over the tumour accompanied with shooting pains, it is a very unpropitious beginning ". Sir James Paget (1874), in the original description of the disease of the nipple and areola which bears his name, described " scattered blotches of redness covering nearly the whole breast ". In 1875 Volkmann applied the name " Mastitis carcinomatosa " to a rapidly-growing carcinoma of the breast occurring in pregnancy or lactation which clinically resembled acute inflammation of the breast.

Other authors, notably Billroth (1879) and Schumann (1911), recorded similar cases of this type occurring in young pregnant or lactating women, but it was not until 1924 when Lee and Tannenbaum published under the title "Inflammatory Carcinoma of the Breast" a series of 28 cases of mammary cancer bearing the superficial appearances of inflammation, that the incidence and characteristics of the disease were comprehensively described. The latter authors demonstrated amongst other things that carcinoma of the breast of the inflammatory type is not specifically associated with the stimulus of pregnancy or lactation and that it may occur in adult women of any age.

Altogether I have been able to trace references in the literature to approximately 220 cases of carcinoma of the breast which are of the inflammatory type, and in this paper I have retained Lee and Tannenbaum's term 'inflammatory carcinoma of the breast' to describe this condition, since amongst the multitude of names so far suggested it still remains the most comprehensive and the most accurate in description.

CASE REPORTS

The histories of the first 2 cases of inflammatory carcinoma of the breast which I saw are presented here in some detail, and these, together with the leading features of the histories of the additional 18 cases, are summarized in *Tables I* and *II*.

FIG. 239.—*Case* 1, showing the condition in both breasts in December, 1948. Both breasts are shrunken and the nipples retracted and encrusted. The skin shows areas of congenital leucoderma on the breasts and right arm, as well as blotches of redness and œdema, especially just internal to the left nipple.

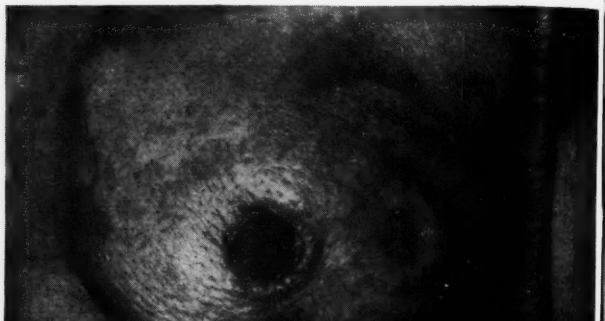

FIG. 240.—*Case* 1. Close-up view of left breast, to show the telangiectases just above the nipple.

Since this first large series of Lee and Tannenbaum many case reports of inflammatory carcinoma of the breast have appeared in the literature, unfortunately under a large variety of descriptive titles, each derived from one of the clinical or pathological manifestations of the disease. The term 'erysipelas carcinomatosum' was introduced by Küttner (1924) 'sub-epidermoidal carcinoma' by Fischer (1926, 1927, 1931), 'carcinoma erysipelatodes acutum' by Rasch (1931), and 'carcinoma telangiectaticum' by Parkes Weber in 1933.

In 1937 Dawson and Shaw, of Edinburgh, published a paper containing reports of 8 cases, one of which was described in detail from the clinical and pathological aspects. They questioned the desirability of applying to this condition a specific title and so promoting it to the status of a distinct pathological entity, but suggested that the importance of the skin lesion lay in its resemblance to primary skin affections or mammary inflammation and the risk of consequent errors in diagnosis and treatment.

In the last ten years, apart from numerous isolated case reports, only two large series of cases of inflammatory carcinoma of the breast have been published: that of Taylor and Melzer (1938), who presented 38 cases, and more recently that of Meyer, Dockerty, and Harrington (1948), who recorded 74 cases selected from the records of the Mayo Clinic over thirteen years.

Case 1.—Mrs. A. B., aged 48, an obese housewife, was first seen at Hammersmith Hospital in July, 1947, when she complained of several firm mobile enlarged glands in her left axilla, gradually increasing in size and present for one month. There were no other complaints. She had breast-fed three children and both her parents had died of cancer—her father of cancer of the colon and her mother of cancer of the stomach. On examination at this time no clinical evidence of disease could be found to account for the lymph-node enlargement. The breasts were normal in appearance, the blood-count within normal limits, Wassermann reaction negative, the sputum clear, and a chest radiograph revealed no abnormality.

On July 22, one of the enlarged axillary glands was removed for biopsy and the patient was discharged from hospital two days later whilst awaiting the report on the gland section. This stated "The gland is enlarged from a diffuse infiltration by isolated cells. These have the characters of epithelial cells and I think that this is an unusual type of carcinomatous invasion. It is difficult to suggest an origin for these invading cells, but certain features suggest a squamous carcinoma". (C. V. H.)

The patient, sent for immediately and advised to come into hospital for further investigation and treatment, refused to come at that time, and was not seen again until more than one year later, in September, 1948. She then reported to the out-patient department of her own accord complaining of a hardness which had developed in the previous twelve months in both breasts. On examination her general condition was excellent. Locally the breasts were shrunken, retracted, and covered by a thickened

œdematous skin showing orange-peel dimpling, diffuse blotchy redness, and scattered telangiectases (*Figs.* 239, 240). Both nipples were retracted and covered with dried secretions. On palpation the breasts were replaced by hard masses fixed to the chest wall and overlying skin. Large, hard, mobile glands were felt in both axillæ, in both supraclavicular regions, and in the right suboccipital region. The arms were moderately swollen by a brawny œdema. Elsewhere nothing abnormal was discovered. A radiograph of the chest showed no abnormality. A biopsy of the left breast and overlying skin was taken and the report stated :—

" 1. In the breast there is a duct papilloma and some intraduct carcinoma. In addition, the whole specimen is diffusely infiltrated by cancer cells which are infiltrating as single cells and causing a fibrous stromal reaction.

" 2. Section of the skin shows the epidermis free of tumour. The dermis is invaded by lymphatic permeation of cancer cells and to a lesser extent by a diffuse single-cell type of invasion. There is also some reactionary lymphocytic permeation. The subcutaneous fat shows much less invasion." (C. V. H.)

A diagnosis of inflammatory carcinoma of the breast was made and the patient was seen in consultation with the radiotherapists, but owing to the diffuse spread of the growth neither radiotherapy nor surgery was advised, but an attempt at palliation was recommended in the form of oöphorectomy and testosterone therapy. The patient agreed to this and on Jan. 11, 1949, a bilateral oöphorectomy was performed with the implantation of 1000 mg. of testosterone in the abdominal wall.

This procedure appeared to produce only a transient improvement in the œdema, which had by this time become noticeable in her face and neck. No improvement was observed in the state of the tumour itself, which continued to spread progressively in the skin of the thorax to fix the chest wall in a cuirass of tough, red, leathery induration. Pleural and mediastinal metastases followed with pleural effusion and atelectasis, and on March 15 the patient died in hospital from the effects of the intrathoracic deposits. Permission for post mortem was refused by her relatives.

The duration of life from the onset of symptoms was twenty-one months.

Case 2.—Mrs. E. S., aged 61, a widow, was referred to us on Jan. 6, 1949, with a history of swelling and tightness of her right arm, and a painful lump in the right axilla, both present for six weeks. There were no other complaints. She had breast-fed two children and there was no family history of cancer.

On examination her general condition was that of a fit, obese, elderly woman with large pendulous breasts. Locally, the right breast was visibly enlarged and, surrounding the nipple, which was normal, was a large irregular area of redness in the skin and widespread œdema of the skin with orange-peel dimpling (*Fig.* 241). On palpation a firm mass 3 × 3 cm. was felt in the lower outer quadrant of the right breast, not attached to the underlying structures but showing early fixation to the skin.

In the right axilla the medial group of lymph-glands had formed a large fixed mass with evidence of commencing suppuration and break-down. The right arm was swollen by a boggy lymphœdema. The left breast and axilla were normal. No supraclavicular glands were palpable. Elsewhere nothing abnormal was discovered. A provisional diagnosis of inflammatory carcinoma of the breast was made and on Jan. 7 an excision biopsy of the mass in the right breast was performed to confirm the diagnosis. At the same time the suppurating mass in the right axilla was incised and pus was evacuated, which gave a growth of *Staph. aureus* on culture. The pathologist's report on the section stated : " A spheroidal-cell carcinoma widely infiltrating with relatively scanty amount of stroma supporting it. The cells are growing in sheets and columns, but here and there form tubular structures. Mitoses are fairly frequent." (C. V. H.)

On Jan. 29 the patient was seen at the combined surgical-radiotherapeutic conference and it was recommended that a course of radiotherapy with œstrogen implantation be given. Therefore between Feb. 7 and April 20 a full course of deep X-ray therapy was applied to six thoracic fields with the 220-kv. apparatus, with the result that the axillary mass disappeared. The patient's pain was partially relieved, but in the breast itself there was no appreciable improvement of the condition. By May 16 the patient was cyanotic and dyspnœic and complained of pain between the shoulder-blades. The erythema had by this time spread to the opposite breast, where there was also marked *peau d'orange*. There were signs of a pleural effusion and the liver was enlarged to two finger-breadths below the costal margin. X-ray films at this date confirmed the presence of extensive pleural and parenchymatous involvement on both sides of the chest, with metastases in the 7th rib on each side and in the pedicle of the 4th thoracic vertebra.

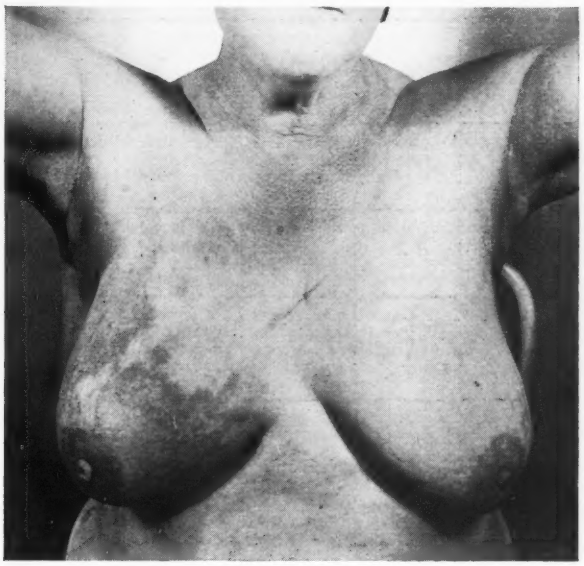

FIG. 241.—*Case* 2. Condition of the breasts in February, 1949. The right breast is enlarged and covered by a raised œdematous erythema which has spread as an irregular sheet and as separate blotches.

On May 25 the patient died at home from the effects of intrathoracic metastases. No post-mortem examination was carried out. Duration of life from the onset of symptoms, seven months.

DISCUSSION

Types.—Inflammatory appearances in the skin may develop in a breast the seat of any variety of mammary cancer and may arise at any time during the course of the disease.

Two arbitrary clinical types of inflammatory carcinoma of the breast are described : The primary type, in which the inflammatory changes appear simultaneously with the carcinoma in an otherwise normal breast ; and the secondary type, in which the inflammatory manifestations appear in a breast already the seat of a long-standing carcinoma or in the mate of such a breast or following a mastectomy for a non-inflammatory cancer of the breast. On

Table I.—PRIMARY INFLAMMATORY

Case and Hospital Number	Age	Single or Married	Children Breast-fed	History of Trauma	Date of Initial Symptoms	Initial Symptoms	Initial Treatment	Date of Arrival in Hospital
1 (70737)	48	M.	3	—	June, 1947	Hard enlarged glands in left axilla	Biopsy of axillary glands	July, 1947
2 (74020)	61	M.	2	—	Nov., 1948	Swelling of right arm and a mass in right axilla	Biopsy of a small mass in right breast	Dec., 1948
3 (82522)	50	M.	—	—	April, 1947	Inflamed painful right breast	Penicillin injections for 'mastitis'	Jan., 1948
4 (82671)	37	M.	—	—	Dec., 1947	Swelling and pain in right breast	—	Jan., 1948
5 (95083)	54	M.	2	—	Sept., 1947	Swelling in right axilla. Painful red swelling in right breast	Biopsy of mass in right breast	Jan., 1949
6 (98879)	64	M.	6	Yes	Feb., 1948	Painful swelling of left breast	Incision and drainage of 'breast abscess'	April, 1949
7 (92009)	62	S.	—	—	May, 1947	Lump in left breast	—	Oct., 1948
8 (97760)	73	S.	—	—	Sept., 1948	Painful lump in right breast	—	March, 1949
9 (82664)	81	M.	11	Yes	Feb., 1947	Loss of use of right arm. Lump in left breast	—	Feb., 1948
10 (50280)	59	M.	2	Yes	May, 1948	Tender lump in right breast	—	Nov., 1948
11 (92521)	69	S.	—	—	Oct., 1948	Mass in right axilla. Burning pain in right breast	—	Nov., 1948
12 (90080)	66	S.	—	—	May, 1948	Painful lump in right breast	—	Aug., 1948
13 (88835)	73	M.	4	—	July, 1947	Lump near left nipple, then bleeding from nipple, then painful red swelling left breast	Simple mastectomy elsewhere, April, 1948	July, 1948
14 (98881)	60	M.	2	—	March, 1949	Lump in left axilla	Biopsy of axillary gland mass	April, 1949
15 (80363)	65	M.	3	—	July, 1947	First painful enlargement of right breast. Then redness and a lump in breast	Kaolin poultices and then later a right radical mastectomy	Nov., 1947

CARCINOMA OF BREAST

CONDITION ON ARRIVAL IN HOSPITAL	PATHOLOGICAL TYPE OF PRIMARY TUMOUR	FINAL TREATMENT	RESULTS OF TREATMENT, COURSE OF DISEASE	DURATION OF DISEASE IN MONTHS
In Sept., 1948, 14 months after gland biopsy, both breasts replaced by fixed hard masses. Redness, œdema, and telangiectases in skin. Bilateral axillary and supraclavicular gland involvement	Intraduct carcinoma	Bilateral oöphorectomy, testosterone implant	Transient slight improvement in the œdema, but rapid spread of the growth. Died from the effects of intrathoracic metastases, March, 1949	21
Right breast enlarged; small mass in lower outer quadrant. Patchy diffuse redness and œdema of skin. Fixed mass of suppurating glands in right axilla. Œdema right arm	Spheroidal-cell carcinoma	Deep X-ray therapy	Slight local improvement only, but rapid spread of growth to opposite breast. Intrathoracic secondaries. Died, May, 1949	7
Right breast enlarged. Skin red and œdematous. Right supraclavicular glands ++. Œdema right arm	Carcinoma simplex with intraduct spread	Deep X-ray therapy; stilbœstrol	Temporary disappearance of tumour mass in right breast, but rapid recurrence and spread to opposite breast. Died, Sept., 1948	18
Right breast enlarged by a large fixed mass. Skin redness. Right axillary glands ++	Spheroidal-cell carcinoma	Deep X-ray therapy; radiation menopause; testosterone	Transient improvement in zones irradiated, but rapid recrudescence with spread to opposite breast. Died, May, 1948	6
Right breast replaced by hard shrunken mass. Skin redness and œdema. Fixed hard glands in right axilla	Intraduct spheroidal-cell carcinoma	Pre-operative radiotherapy; simple mastectomy; post-operative radiotherapy	Local disappearance of masses with treatment. Alive in May, 1949, with supraclavicular glands involved on both sides	Alive with residual cancer in 20 months
Left breast replaced by hard fixed growth. Widespread redness and œdema of skin. Both axillary gland groups and left supraclavicular glands involved	Spheroidal-cell carcinoma	Deep X-ray therapy	Temporary decrease in pain and induration in left breast. Later spread to opposite breast and lungs. Died, June, 1949	17
Left breast enlarged by a fixed mass. Skin redness. Outlying nodules of cancer in skin. Left axillary glands involved	Spheroidal-cell carcinoma	Deep X-ray therapy. Œstradiol implants	Transient improvement in treated areas. Rapid growth outside treated areas—spread to opposite breast, lungs, and bones. Died, May, 1949	24
Large fixed mass in right breast. Widespread redness and œdema of skin with superficial excoriation. Right axillary gland enlarged	Ill-differentiated adenocarcinoma	Deep X-ray therapy	Temporary local improvement. Later spread to opposite breast	Alive with advanced cancer in 10 months
Fixed hard mass in left breast. Slight superficial excoriation. Large mass in right supraclavicular region. Widespread patchy redness in thoracic skin. Left axillary glands hard and fixed. Right arm œdematous and paralysed	No biopsy performed	Palliative local X-ray therapy to mass in right supraclavicular region	Mass in shoulder shrunken and painless. Elsewhere progressive spread of growth. Died, Oct., 1948	20
Hard mass in right breast. Redness and œdema of skin. Bilateral axillary glands ++. Right supraclavicular glands ++	Spheroidal-cell carcinoma	Simple mastectomy. Pre- and post-operative radiotherapy	Local disappearance of tumour in treated areas. Later metastases appeared in bones, liver, and lungs. Died, April, 1949	11
Diffuse massive right breast. Œdema and redness of mammary skin. Glands involved in both axillæ	Spheroidal-cell carcinoma	Simple mastectomy. Pre- and post-operative radiotherapy	Local improvement in skin condition and mass in axilla. Later residual cancer mass in both axillæ. Lymphœdema right arm	Alive with residual cancer in 9 months
Hard fixed mass in right breast. Surrounding redness and cancerous skin nodules. Right axillary gland enlarged	Scirrhous canalicular carcinoma	Local deep X-ray therapy	No response to treatment; rapid spread to bones and viscera. Died, Nov., 1948	6
Left mastectomy scar with mass at upper end. Outlying skin nodules and patchy redness. Left supraclavicular nodes involved	Carcinoma simplex	Deep X-ray therapy; stilbœstrol	Local improvement with radiotherapy, but later spread to opposite breast and cuirass involvement of skin. Died, Feb., 1949	18
Only hard large axillary glands on admission. Five weeks later left breast became swollen, red, and painful	Spheroidal-cell carcinoma	Simple mastectomy; post-operative radiotherapy	Spread to areas outside left breast and involvement of glands in opposite axilla	Alive with residual cancer in 3 months
Healed mastectomy scar. Surrounding skin deposits. Right axillary and supraclavicular masses palpable	Carcinoma simplex	Local deep X-ray therapy	No response to treatment; progressive spread in skin and finally to lungs. Died, Aug., 1948	13

Table I.—PRIMARY INFLAMMATORY CARCINOMA

CASE AND HOSPITAL NUMBER	AGE	SINGLE OR MARRIED	CHILDREN BREAST-FED	HISTORY OF TRAUMA	DATE OF INITIAL SYMPTOMS	INITIAL SYMPTOMS	INITIAL TREATMENT	DATE OF ARRIVAL IN HOSPITAL
16 (70725)	52	M.	4	—	Feb., 1946	Diffuse swelling of right breast	Right radical mastectomy elsewhere	Nov., 1946
17 (93754)	42	M.	3	—	Aug., 1948	Rapidly growing lump in right breast with pain and redness	Poultices and incision of breast	Dec., 1948

Table II.—SECONDARY INFLAMMATORY CARCINOMA

CASE AND HOSPITAL NUMBER	AGE	SINGLE OR MARRIED	CHILDREN BREAST-FED	HISTORY OF TRAUMA	DATE OF INITIAL SYMPTOMS	INITIAL SYMPTOMS	INITIAL TREATMENT	DATE OF ARRIVAL IN HOSPITAL
18 (73819)	56	S.	—	—	Jan., 1946	Lump in left breast	Left radical mastectomy, May, 1946	March, 1947
19 (59302)	66	S.	—	—	June, 1945	Painless lump in left breast	Left radical mastectomy, Nov., 1945	In-patient, Nov., 1945, April, 1947, July, 1947
20 (99350)	46	S.	—	—	May, 1948	Painless lump in left breast	Left radical mastectomy, July, 1948	May, 1949

this basis, 17 of the cases in this series could be classified as primary and 3 of the cases as secondary inflammatory carcinoma of the breast (*see Tables I* and *II*).

Incidence.—From June 1, 1946, to May 31, 1949, a period of three years, 214 cases of proved carcinoma of the breast of all types were admitted to Hammersmith Hospital. Of these, 20 were of the inflammatory variety, constituting 9·3 per cent of all admissions. This is an unusually high incidence compared with those quoted in other series, e.g., 1 per cent in the Mayo Clinic series (Meyer and others, 1948) and 4 per cent in Taylor and Melzer's (1938) series. This high incidence may be explained by the fact that Hammersmith Hospital houses a Medical Research Council Radiotherapeutic Unit, which receives a disproportionately large number of patients with advanced cancer of the breast who have been referred from other hospitals for post-operative or palliative radiotherapy, and it is amongst this group of advanced cases that the inflammatory type of cancer is predominantly found.

Sex and Age Incidence.—All the patients in this series were women. Inflammatory carcinoma of the breast is rare in the male; I have been able to find reports in the literature of 4 cases arising in men, 1 by Rotter (1936), 1 by Schreiner and Volavsek, quoted by Freeman and Lynch (1937), and 2 by Treves (1949).

The age incidence in our series followed that of carcinoma of the breast generally, the youngest patient being 37 years old and the oldest 81 years. The average age was 59·2 years.

Pregnancy and Lactation.—In this series none of the cases of inflammatory carcinoma arose during pregnancy or lactation. Of our 20 cases, 11 had breast-fed their children many years before the onset of the disease, and the remaining 9 patients had never been pregnant. Similarly, amongst the 140 cases of inflammatory carcinoma collected from the three largest reported series (Lee and Tannenbaum, Taylor and Melzer, and Meyer and others) only 2 patients (1·4 per cent) were either pregnant or lactating at the time of the disease. Carcinoma of the breast of all varieties is uncommon during pregnancy or lactation: Harrington (1937) records 92 cases occurring in pregnancy or lactation amongst 4628 cases of breast cancer operated on at the Mayo Clinic—an incidence of approximately 2 per cent.

Nor is the mammary cancer of pregnancy or lactation always inflammatory in type. Taylor and Melzer (1938) analysed the records of 205 cases of carcinoma of the breast arising in women during pregnancy and lactation and only 45 (22 per cent) were of the inflammatory type. Hence the incidence of inflammatory carcinoma of the breast occurring in pregnancy or lactation must be very small indeed,

CARCINOMA OF BREAST, *continued*

CONDITION ON ARRIVAL IN HOSPITAL	PATHOLOGICAL TYPE OF PRIMARY TUMOUR	FINAL TREATMENT	RESULTS OF TREATMENT, COURSE OF DISEASE	DURATION OF DISEASE IN MONTHS
Right mastectomy scar with surrounding skin deposits. Large hard mass in left breast with overlying redness and œdema. Left axillary glands ++	Encephaloid carcinoma	Deep X-ray therapy	Transient mild local improvement; later, rapid spread, especially to liver. Death from hepatic failure, Jan., 1947	11
Large fixed mass in right breast. Discoloured skin over breast. Axillary and supraclavicular glands involved. Œdema right arm. Gross enlargement of liver by cancer	Undifferentiated carcinoma simplex arising from ducts	Deep X-ray therapy	Slight shrinkage of primary tumour with therapy, but died Feb., 1949, with metastases in liver and thorax	6

CARCINOMA OF BREAST

CONDITION ON ARRIVAL IN HOSPITAL	PATHOLOGICAL TYPE OF PRIMARY TUMOUR	FINAL TREATMENT	RESULTS OF TREATMENT, COURSE OF DISEASE	DURATION OF DISEASE IN MONTHS	
				From onset of symptoms	From onset of redness
Left mastectomy scar surrounded by widespread œdema and redness. No lymph-glands palpable; metastasis in thoracic spine	No report available on specimen	Deep X-ray therapy to spine and chest; stilbœstrol	Pain of spinal deposit relieved. Mild transient improvement in skin. Metastases in lungs. Died, Dec., 1947	20	9
Nov., 1945: Scirrhous mass, left breast April, 1947: Multiple skin deposits in chest; hard glands in right axilla July, 1947: Hard mass in right breast. Marked skin redness	Spheroidal-cell carcinoma	Local deep X-ray therapy; stilbœstrol. July, 1947: Right simple mastectomy	Progressive spread, in spite of therapy, to opposite breast and pleura. Died, Nov., 1948	41	16
Healed mastectomy scar. Large patches of surrounding redness with skin nodules. Fixed hard masses in left axilla	Carcinoma simplex	Radiotherapy to skin and tumour masses	Masses disappeared with therapy but redness and tumour appeared later in right breast	Alive with residual cancer in: 13 months	5 months

probably constituting under 0·5 per cent of all cancers of the breast.

Therefore, although there is no evidence that the inflammatory type of carcinoma is specifically associated with pregnancy or lactation, it is evident that when cancer of the breast does arise in a woman during pregnancy or lactation it has an increased chance of being of the inflammatory type.

Trauma.—Three of our 20 patients claimed a definite injury, presumably coincidental, to the affected breast prior to the onset of symptoms.

Symptoms and Signs.—A list of the initial symptoms in the cases in this series is given in *Tables I* and *II*. Analysis of these shows that in the primary cases, a painful diffuse enlargement of the breast was the commonest initial symptom and a rapidly growing localized mass in the breast was the second commonest symptom. In describing the appearance of the breast the patient frequently referred to the discoloration, redness, or inflammatory change in the overlying skin.

Pain in the breast was present at the onset in 9 out of the 17 primary cases and was described as "shooting", "stabbing", or "burning". Later in the disease pain was commonly present and was then usually the result of bony metastases. One patient (*Case* 1) was remarkably free from pain throughout the disease.

Five patients complained of enlarged axillary lymph-nodes at the onset of the disease and after a variable interval of weeks or months symptoms developed in the breast. Other less frequent initial symptoms were brawny enlargement of the arm, bleeding from a retracted nipple, and paralysis of the arm from involvement of the brachial plexus by growth.

On examination the redness in the breast which is characteristic of inflammatory carcinoma varied in tint in different patients from a fiery scarlet, through a livid bruised colour, to a pale rosy pink. This redness could be obliterated by pressure, the colour returning after the release of pressure, and in the dependent parts of the breast the redness sometimes took on a deeper hue. The areas of redness spread centrifugally from the affected breast around the chest wall to the back and across the middle line to the opposite breast. The areas were usually confluent and spread as an irregular sheet with raised edges—hence the similarity to erysipelas—or else the redness took the form of irregular blotches of erythema scattered on the chest around the affected breast. In several patients the confluent and blotchy forms of erythema appeared simultaneously (*see Fig.* 241). In one patient (*Case* 1) the thoracic skin showed, in addition to the redness, widespread violaceous telangiectases—the appearance which led Parkes Weber to the use of the term 'carcinoma

telangiectaticum' (*see Fig.* 240). Invariably associated with the cutaneous discoloration, but to a greater or lesser extent, there was an indurated lymphatic œdema of the skin giving the typical orange-peel dimpling effect. In several cases this œdema accompanied by the redness spread around the chest wall to produce a raised tough morocco-leather-like induration of the skin which ultimately fixed the thorax in a veritable cuirass and caused the patient to become dyspnœic.

FIG. 242.—*Case* 6. Lateral view of left side of chest showing the superficial excoriation of the skin of the breast due to irradiation. A band of raised erythematous œdema has extended laterally to the scapular region beyond the area marked out for irradiation. A recent biopsy wound in the involved skin is shown.

Each of the three patients with secondary inflammatory carcinoma in this series had a radical mastectomy performed previously for a non-inflammatory cancer of the breast and appeared with changes in the skin around the mastectomy scar such as have just been described. In addition these patients showed nodules of cancer visible in the skin within or remote from the inflammatory areas (*Fig.* 244).

Retraction and distortion of the nipple occurred in 11 out of the 20 cases, and in 4 of them was associated with a serous discharge from the nipple with incrustation (*see Fig.* 239).

No true case of Paget's disease of the nipple was found either clinically or histologically in this series, although inflammatory cancer of the breast has been described in cases with Paget's disease of the nipple, notably by Paget himself.

Apart from the desquamation produced by radiation, no ulceration of the skin occurred in 15 of the 20 cases in this series. In the remaining 5 an area of superficial excoriation of the skin appeared over the original centre of the lesion in the final stages of the disease. None of our patients developed the crateriform ulcer commonly seen in advanced scirrhous cancer. Inflammatory carcinoma of the breast

FIG. 243.—*Case* 8. Condition in June, 1949, two months after completing radiotherapy. Showing the right breast contracted and the nipple retracted. The tumour has ulcerated through the skin to a small extent just medial to the nipple and a large superficial nodule of growth is projecting under the skin above the nipple. The skin is œdematous and pigmented and is bright red and hot over the greater part of the breast. The redness is extending as streaks across the middle line on to the opposite breast.

FIG. 244.—*Case* 19. Secondary inflammatory carcinoma of the breast. Areas of raised red œdema with cancerous nodules in the skin are seen spreading from both mastectomy scars to encircle the chest *en cuirasse*.

usually causes the death of the patient before massive ulceration can take place.

There is a marked tendency for inflammatory carcinoma to spread to the opposite breast. This high incidence of bilateral involvement has been emphasized by most recent authors and is due to lymphatic spread of the growth across the middle line of the chest. Of 15 patients who have died, 10 showed spread to the opposite breast before death, and of the 5 patients alive at the time of writing 3 have already developed bilateral involvement.

On palpation of the affected breasts, the examining hand commonly discovered a hot, firm, massive tumour fixed to the skin or a diffuse replacement of the whole breast by a fixed, firm mass. Occasionally a small, primary tumour mass was felt in the breast when the patient was first examined, and in 3 cases no tumour or any abnormality was discovered in the breasts at all, but enlarged axillary lymph-nodes were present. The regional lymph-nodes (axillary, supraclavicular, or both) were palpably enlarged and hard in 18 out of 20 cases early in the disease, and sooner or later the contralateral regional lymph-nodes became invaded by growth. In 5 patients the axillary-node swelling was amongst the earliest symptoms of the disease.

Distant visceral or skeletal metastases in the primary cases were detectable on admission to hospital either clinically or radiologically in 3 patients (*Cases* 9, 12, and 17), the secondary deposits lying in the shoulder-girdle bones, the lungs, and the liver respectively.

Diagnosis and Differential Diagnosis.—The diagnosis of primary inflammatory carcinoma of the breast is of interest in view of the errors which may be made in confusing the overlying inflammatory signs with those of acute mastitis or of a dermatological condition of the mammary skin.

Of the 17 primary cases in this series, 10 were correctly diagnosed as mammary cancer when first seen. Of the remaining 7 cases, 4 were initially diagnosed by the medical attendant elsewhere as acute mastitis, and as a result were treated by incisions, poulticing, or penicillin therapy until such time as the true nature of the disease became obvious.

Three patients presented with malignant enlargement of the axillary lymph-nodes with no clinically demonstrable primary source for the growth and diagnosis was delayed until obvious signs of breast involvement appeared.

The most frequent misdiagnosis in the primary cases was ' acute mastitis ' or ' breast abscess ' and the error is an easy one to make, but due consideration of the following points may help the surgeon to arrive at a correct diagnosis.

Acute mastitis in an adult woman occurs with few exceptions in the early months of lactation and is associated with localized tenderness in the breast, pyrexia, leucocytosis, and often with generalized toxæmia and rigors. The skin overlying an acute mastitis may show thickening and œdema in the early stages, but the lesion should, in the course of a few days, either show resolution or form an intramammary abscess over which the skin becomes shiny, red, and smooth.

Inflammatory carcinoma of the breast occurs most frequently in the fourth to the sixth decades in otherwise fit non-lactating women. It is characteristically non-tender and is not associated with pyrexia, leucocytosis, or toxæmia. The skin lesion is diffuse, may extend beyond the confines of the breast, and is associated with widespread œdema of the skin and commonly with retraction of the nipple. Its progress is relatively slower than that of an acute mastitis and is unaffected by treatment with the antibiotics.

When the diagnosis still remains in doubt, it is wise to adopt the principle that an inflammatory lesion of the breast which does not show signs of resolution under treatment in ten to fourteen days should be submitted to exploration and biopsy to exclude the presence of cancer. This procedure will also serve to bring to light those rare conditions of the breast in which a mass may sometimes be associated with inflammatory appearances in the overlying integument, namely chronic mammary abscess, tuberculosis of the breast, plasma-cell mastitis, gumma, sarcoma, and Hodgkin's disease (lymphadenoma).

Three patients with proved malignant axillary-node enlargement as an isolated clinical finding presented difficulty in diagnosis. In such cases one must carefully exclude the presence of malignant neoplasm in the skin of the upper limb and thorax, and the breasts must be examined with meticulous care for the presence of a small tumour. If these examinations prove negative then the bronchial tree, alimentary tract, and pelvic organs should be investigated for cancer, and if this search also reveals no evidence of growth, one must postulate that the most likely source of the primary growth is the breast, the tumour still being in a subclinical form.

The three cases of secondary inflammatory carcinoma in this series were correctly diagnosed when first seen as cancerous infiltration of the skin and treated appropriately. It is apparent that in secondary inflammatory carcinoma of the breast misdiagnosis is less likely to occur, as a previous diagnosis of cancer has usually already been established, but the appearances may nevertheless be confused with those of radiation erythema, wound infection with cellulitis, or with true erysipelas.

To avoid such misdiagnosis it should be noted that radiation erythema only appears in those areas of skin which have received irradiation. The erythema normally takes from ten to fourteen days from the commencement of irradiation to appear and the skin may undergo desquamation or pustulation. Fading occurs about ten days after the last application and a mottled brownish pigmentation with or without telangiectases remains in the skin.

Pyogenic infection of a mastectomy wound may be easily distinguished from secondary inflammatory carcinoma by the presence of early throbbing pain and tenderness in the wound, the pyrexia and leucocytosis, and the discharge of infected serous or purulent exudate from the wound edges.

Finally true erysipelas of the breast is extremely rare but can produce the identical naked-eye appearances in the skin with those of inflammatory carcinoma. In untreated erysipelas the patient is extremely ill, with a profound generalized toxæmia, high pyrexia, and leucocytosis, and, unlike inflammatory carcinoma, the condition will show a dramatic response to treatment with the antibiotics.

Pathology.—At the time of writing (July, 1949) 15 of the 20 cases in this series were dead and 5 were alive. Breast biopsy material was obtained from 14 of the 15 patients who have died and a full post-mortem examination was performed on 4 of these patients. Biopsy material was also collected from the breasts of the 5 living patients, and in addition sections of involved skin have been taken and examined in 5 cases.

The Primary Tumour.—A study of the primary tumour in the breast in this series reveals that inflammatory carcinoma may occur in a breast irrespective of the histological variety of the primary growth within it. Reference to *Tables I* and *II* will show the description applied to the primary growth in each instance by the pathologist. Adenocarcinoma, intraduct carcinoma, spheroidal-cell carcinoma, etc., are represented. This confirms the findings of previous authors, who have drawn attention to the variability of the type of primary growth in cases of inflammatory carcinoma of the breast.

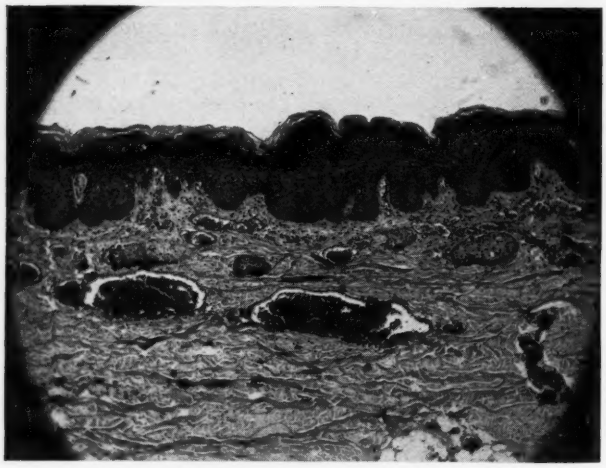

FIG. 245.—*Case* 7. Photomicrograph from skin, showing thickening of the epidermis due to acanthosis and hyperkeratosis, subepidermal lymphatic permeation by clumps of cancer cells, and distended blood-vessels in the subpapillary region. (× 32·5.)

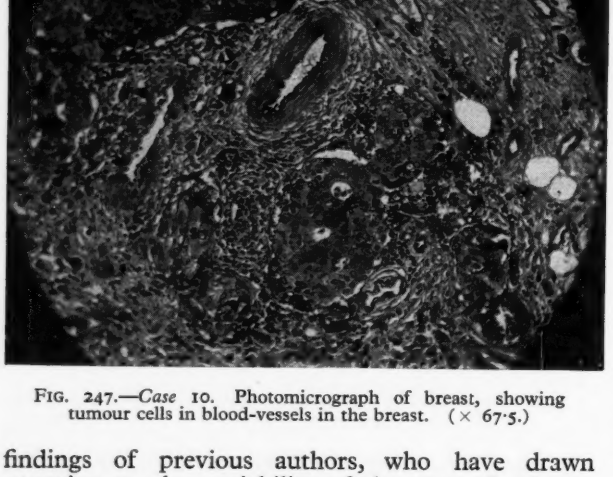

FIG. 247.—*Case* 10. Photomicrograph of breast, showing tumour cells in blood-vessels in the breast. (× 67·5.)

The Mode of Spread.—The pathological feature which is characteristic of inflammatory carcinoma of the breast is the manner in which it spreads to involve the skin, so producing the clinical appearances previously described. The predominant mode of spread in the skin is by a rapid permeation of the subepidermal lymphatic channels, and this is but a superficial manifestation of the underlying rapid permeation by cancer cells of the breast substance itself and the adjacent tissues.

The pathological changes in inflammatory carcinoma have been studied for over half a century. Thomas Bryant in 1887 first described the spread of growth through the lymphatics and blood-vessels in "acute brawny cancer", his term for what is now called 'inflammatory carcinoma of the breast'. Later, Leitch (1909) gave a clear account of the microscopical spread of "acute mammary cancer" and described the characteristic sub-epidermal lymphatic permeation. In addition he gave the first true account of the mechanism of the production of the orange-peel dimpling.

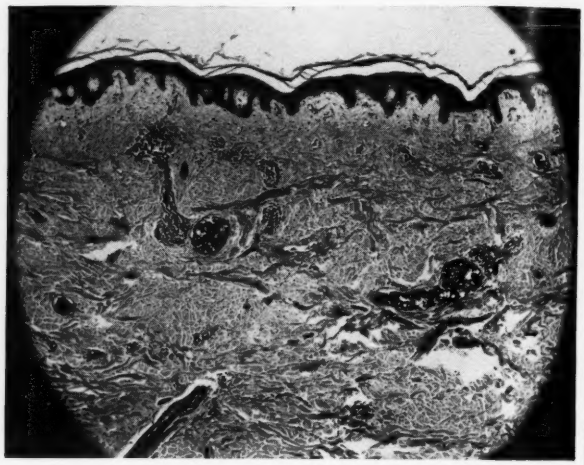

FIG. 246.—*Case* 1. Photomicrograph of the skin, showing normal epidermis and dilated subepidermal lymphatics containing cancer cells and permeated by lymphocytes. (× 32·5.)

Küttner (1924), in his report on 3 cases of "erysipelas carcinomatosum", described the presence of tumour in blood-vessels in the dermis and claimed that the erysipelatoid appearance in the skin was a consequence of the spread of tumour in these superficial vessels. Since Küttner's report, other authors have described the presence of tumour cells either predominantly in the blood-vessels of the skin (Parkes Weber, 1933; Freeman and Lynch, 1937; Dawson and Shaw, 1937), or predominantly in the subepidermal lymphatics (Lee and Tannenbaum, 1924; Pfahler and Case, 1936; Meyer and others, 1948).

This apparent controversy about the channels of spread in inflammatory carcinoma was occasioned partly by the fact that in microscopical sections of involved skin it is usual to see clumps of tumour cells lying within endothelial-lined spaces in the subepidermal layers, and it is difficult to decide whether these spaces are lymphatic or vascular in origin. Camiel and Bolker (1941), in an attempt to determine the origin of these spaces, examined over 200 serial sections of involved skin from two cases of inflammatory carcinoma of the breast, failed to find erythrocytes within tumour-containing spaces, and concluded that the permeated spaces were all lymphatic.

In our series, 5 patients had portions of involved skin submitted to section and this revealed the

characteristic subepidermal lymphatic permeation, but no evidence could be found of tumour cells within the blood-vessels of the skin, although other sections taken through breast, liver, and lungs of our patients did show occasional areas with definite involvement of blood-vessels by growth (*Fig.* 247).

In addition to the lymphatic permeation, the skin sections also demonstrated the following pathological features (*Figs.* 245, 246) :—

1. In some sections, a diffuse infiltration of the subepidermal connective tissues by isolated cancer cells which had burst out of the small lymphatics.
2. Perilymphatic collections of lymphocytes and plasma cells.
3. A variable but definite dilatation of the small subcutaneous blood-vessels (capillaries and venules) in the red areas of skin.
4. Freedom of invasion of the epidermis by cancer cells, thus distinguishing it from Paget's disease.
5. In some places a distinct thinning of the epidermis and in others a distinct thickening caused by acanthosis and hyperkeratosis.

The conclusion can be drawn that lymphatic channels appear to convey the tumour in the dermis and that spread in the skin through the blood-vessels, although it has been shown to occur, is, relatively, an uncommon mode of spread in inflammatory carcinoma of the breast.

The appearance of redness in the mammary skin and its environs is due to the dilatation of the minute subpapillary blood-vessels, but the exact mechanism of its production in inflammatory carcinoma is still a matter of speculation. It has been suggested (Taylor and Melzer, 1938; Meyer and others, 1948) that the redness is a manifestation of passive hyperæmia resulting from the increased pressure within the breast from lymphatic obstruction and stasis.

Passive hyperæmia alone, however, will not account for all the appearances in the skin. In favour of this passive origin for the skin redness is the observation that the depth of colour may be affected by gravity, being deeper in the dependent parts of the breast and tending to fade with recumbency. Against a completely passive origin for the redness is the fact that these red areas are distinctly hotter to touch in many patients than the surrounding skin, a heat which must be due to increased blood-flow to the skin, and therefore to active arteriolar dilatation. It is probable that the local arteriolar dilatation is an active response to the presence of subepidermal cancer, and that the redness and heat in the skin is partly an active, partly a passive, vascular phenomenon.

Regional lymph-node involvement occurs very early in the disease, followed soon after by spread from the primary growth into the thorax, to the pleura, lungs, mediastinum, and bony thoracic cage, and finally to distant viscera and skeletal structures. Intrathoracic spread was proven clinically, radiologically, or at post-mortem in 10 of the 15 patients who died. In 6 of the deaths, secondary deposits of cancer in the liver were demonstrated clinically or at post-mortem and in 2 of these patients the cancerous involvement of the liver was so massive as to produce liver failure with consequent death. In 5 of the deaths, radiological or post-mortem evidence of skeletal metastases was discovered; the ribs, spine, sternum, clavicle, head of humerus, and upper end of femur being variously involved.

Treatment and Its Results.—Reference to *Tables I* and *II* will show the method of treatment applied in each case, together with the results obtained. The appropriate combination of therapy was selected according to the merits of each case, and it will be seen that in 10 of our 20 cases surgical procedures, viz., radical or simple mastectomy, were combined with radiotherapy given pre- or post-operatively, or both. In a further 9 cases surgery was considered inadvisable owing to the widespread extension of the growth, and treatment was carried out solely by palliative deep X-ray therapy. In 7 of our 20 cases, hormone therapy was given in addition, either as œstrogen to the postmenopausal patients, or as testosterone to the premenopausal patients. In two of the premenopausal patients the menopause was induced, in one by oöphorectomy and in the other by irradiation.

The spread of inflammatory carcinoma of the breast is rapid, but is so insidious that by the time the patient has reached the surgeon the disease has commonly spread beyond the anatomical limits of a radical mastectomy and as a consequence the prognosis is a dismal one. Whichever combination of therapy was applied in this series, no 'cure' was obtained. Fifteen of the 20 patients died of cancer; 5 patients are still alive and have all had a full initial course of treatment, but in spite of it still show clinical evidence of residual cancer and are expected to succumb to its effects in the near future. There was no significant variation in the duration of the disease whichever combination of treatment was applied.

The figures for duration from the onset of symptoms to the date of death in the 13 fatal primary cases varied from 6 months to 24 months (average duration 13·7 months). Two secondary cases died in 9 and 16 months respectively, calculated from the date of onset of the inflammatory signs.

Radiotherapy commonly caused the primary neoplasm and malignant axillary lymph-nodes to disappear clinically, or at least caused them to shrink to a small volume, but the disease reappeared later, usually outside the irradiated areas. In 2 patients no response whatever resulted from radiotherapy applied to the primary growth. Where radiation was given for secondary bone metastases pain was significantly relieved. There is no evidence in this series that hormones produced any marked affect upon the disease, although in *Case* 1 a slight improvement was noticed in the patient's facial œdema for a few days following the implantation of testosterone, but soon after the patient went rapidly downhill.

The literature contains only isolated reports of 5-year survival. One case reported by Bloodgood (1908) was free of recurrence 5 years after radical mastectomy. A second case, Learmonth's (1916), was free of recurrence after 7 years, and 3 cases from the Mayo Clinic (Meyer and others, 1948) have survived at least 5 years after radical mastectomy. It must be noted that all these five survivals were treated by radical mastectomy, a justification perhaps for

advocating radical surgery in inflammatory carcinoma of the breast. Even so, surgery only offers the chance of prolonged survival when it is done early in the disease, when the growth is mobile and still confined to the breast, and the redness and œdema of the skin lie comfortably within the limits of a radical mastectomy. Such a presentation is unfortunately rare, but when it does arise, radical mastectomy is the most hopeful procedure and should be carried out with the removal of a substantial margin of healthy-looking skin around the red œdomatous zone.

In most other cases palliation by radiotherapy will offer the patient a prognosis of up to 2 years of life.

SUMMARY

1. Inflammatory carcinoma of the breast is an uncommon clinical variety of mammary cancer in which cutaneous infiltration by growth produces the signs of inflammation in the involved skin.

2. Twenty cases of inflammatory carcinoma are presented and the literature on the condition is briefly reviewed.

3. Inflammatory cancer may arise in women at any age and is not specifically associated with pregnancy or lactation.

4. The disease may be primary, arising in a normal breast, or secondary, arising in a breast already the seat of a non-inflammatory cancer.

5. The skin signs are predominantly redness and œdema. The redness varies from a pale pink to a fiery scarlet and spreads peripherally in irregular sheets or as isolated blotches. The red areas in the skin are sometimes raised and hot to the touch. Co-extensive with the redness there is an œdema of the skin with orange-peel dimpling.

6. Crateriform ulceration does not occur, but invasion of the opposite breast is common.

7. Diagnosis may be delayed by confusion with other conditions, notably acute mastitis. Four of the 20 patients in this series were treated for acute mastitis for periods until the neoplastic nature of their condition was discovered.

8. If a breast lesion, suspected to be inflammatory, shows no signs of resolution under treatment within 10 to 14 days, it is wise to explore and take a biopsy of the lesion to exclude the presence of carcinoma.

9. The primary tumour in inflammatory carcinoma of the breast may be of any histological variety. The characteristic pathological feature of the disease, however, is the widespread permeation of the subepidermal lymphatics with cancer. No cutaneous blood-vessels were invaded by growth in the sections that were studied from this series.

10. The cause of the skin redness is briefly discussed.

11. The disease spreads rapidly and is usually beyond radical cure when first seen by the surgeon.

12. The duration of life in this series was not significantly affected by variations in the forms of treatment.

13. Fifteen of our 20 patients are dead at the time of writing and the duration of the disease in them varied from 6 to 24 months from the onset of symptoms. Five patients are still alive, but with clinical evidence of residual growth in spite of treatment.

14. The prognosis is bad, and five-year survival is rare. Of approximately 220 cases of inflammatory carcinoma in the literature, only 5 are recorded as having survived 5 years or more.

15. Treatment by radical mastectomy is justifiable in the rare event of the patient being seen very early, but for the majority of patients palliative treatment with radiotherapy is indicated and offers up to 2 years of life.

I am grateful to Dr. Constance Wood for allowing me to publish cases from the M.R.C. Radiotherapeutic Unit. My thanks are also due to Dr. C. V. Harrison and the staff of the Department of Pathology for the reports on the tissue sections.

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CHRONIC PEPTIC ULCER OF THE ŒSOPHAGUS AND 'ŒSOPHAGITIS'

By N. R. BARRETT, London

The terms 'œsophagitis' and 'peptic ulcer of the œsophagus' connote one thing to some people and something quite different to others. Confusion has overtaken us partly because the rich legacy of clinical observations recorded by Morell Mackenzie and his contemporaries have not been sufficiently carefully alined with the recent advances in the pathology of the living œsophagus.

In 1884 Mackenzie defined 'œsophagitis' as "acute idiopathic inflammation of the mucous membrane of the œsophagus giving rise to extreme odynphagia and often to aphagia"; this condition was the entity which surgeons meant when they used the term 'œsophagitis', and in this sense the disease was first named by John Peter Frank in the eighteenth century. In 1722 Boehm described the acute pain which "reached down even to the stomach and which was accompanied by hiccup and a constant flow of serum from the mouth'. In 1785 a physician called Bleuland was struck down with the disease himself and he carefully recorded the course of the malady. In 1828 Billard published a statement concerning the ailments of the newborn, and it was he who first reported 'œsophagitis' in children. In the following year Mondière (1829) wrote a thesis describing an attack of œsophagitis he had experienced personally, and the subject was further illuminated by communications from Hamburger, Padova, and many others.

According to Mackenzie the cause was unknown, but the chief symptom was excruciating burning or tearing pain—odynphagia—induced by any attempt to swallow or any movement of the laryngeal muscles. The patient generally experienced great thirst, but being unable to get relief by drinking, he could but endure the torment. In adults there was constant expectoration of frothy saliva; the patients were not pyrexial, but might become delirious, and Mackenzie, who gave details of 5 personal cases, said that none proceeded to abscess formation or suppuration. He judged the lesion to be diffuse catarrhal inflammation of the mucosa at the *upper* end of the gullet and diagnosis was based upon the extreme pain and the absence of pharyngeal inflammation.

We can be satisfied that Mackenzie was not referring to inflammation the result of swallowed corrosives, nor to the ulceration of specific fevers such as diphtheria; nor to thrush, tuberculosis, actinomycosis, syphilis, or growths. To-day we do not recognize the disease which Mackenzie described, but we use 'œsophagitis' to describe another entity which chiefly affects the *lower* part of the gullet.

In 1900 all inflammatory conditions affecting the gullet were considered as varieties of 'œsophagitis', but it was about this time that one of these began to arouse especial interest. Writing in 1906, Wilder Tileston pointed out that at least twelve different types of *ulceration* could be clearly separated from each other—namely, those due to carcinoma, corrosives, foreign body; those complicating acute infectious diseases, decubitus, aneurysms, catarrhal inflammations; those associated with diverticulum, tuberculosis, syphilis, varicosities, and ulcers due to thrush. Apart from these he drew special attention to *peptic ulcer of the œsophagus*, which he said exactly simulated chronic gastric ulcer. It was a rare but definite entity which had first been described by Albers in 1839 and from then onwards had been occasionally reported by pathologists. Rokitansky had given the weight of his authority to support the view that peptic ulcer of the lower œsophagus existed; it was considered to be due to the presence of gastric juice in the gullet. Tileston, who reviewed the literature, stated that up till 1906 there had been 44 undoubted examples published. The ulcers concerned were generally single, but were often associated with chronic peptic ulcer in the stomach or the duodenum. They were large, penetrating lesions, sometimes 6 to 8 cm. in length, which were disposed longtitudinally but might encircle the gullet, and they were considered to occur in that part of the œsophagus which lay "above the cardiac sphincter". The patients were usually elderly, and many had no symptoms referable to the œsophagus until shortly before admission to hospital. Death generally resulted from perforation either into a large vessel, the pericardium, the mediastinum, or the pleural cavity; some died of pneumonia, but few had symptoms of œsophageal obstruction. The histology of these ulcers was identical with chronic gastric ulcer, and the adjacent mucosa was gastric in type: it was assumed to be 'ectopic' because it lined the lower part of the gut in the mediastinum.

Twenty years later 'peptic ulcer of the œsophagus' became a matter of special interest. The pathologists continued to report isolated examples of chronic peptic ulcer occurring at the lower end of the gullet. Meanwhile clinicians, who were dealing with patients, were also reporting a variety of œsophageal lesions which had been discovered as a result of improvements in radiological diagnosis and in œsophagoscopy.

The confusion in which we find ourselves to-day dates from this time, because the pathologists, the clinicians, and the endoscopists assumed that they understood each other and that they were talking about the same entity when they referred to 'peptic ulcer of the œsophagus' or to 'œsophagitis'. By 1929 it was clear that all was not well, for Chevalier Jackson claimed to have seen 88 cases in 4000 consecutive endoscopies, whereas Stewart and Hartfall (1929) had found but 1 example in 10,000 consecutive autopsies. Since 1929 there have been many important contributions, such as those by Lyall (1937), Chamberlin (1939), Dick and Hurst (1942), and by Allison and Johnstone, of Leeds (1943, 1946, and 1948). None of these authors find themselves in difficulty as to what they mean by 'peptic ulcer of the œsophagus' or 'œsophagitis'.

I submit that the ulcers described by Tileston and, later, by Stewart and Hartfall and by Lyall, are different from those referred to by clinicians such as Allison : that the former are rare and of little clinical significance, whereas the latter are common and important entities. I suggest that the pathology of the former has been tacked on to the symptomatology of the latter, and that chaos has resulted.

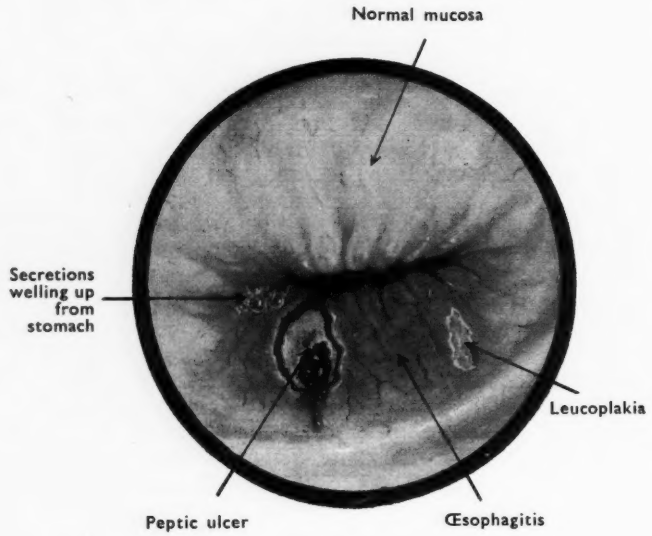

FIG. 248.—Painting to show the characteristic appearances of ' reflux œsophagitis ' and ' peptic ulcer of the œsophagus ' as seen at endoscopy. The floor of the ulcer is partially covered by a slough and the base is composed of granulation tissue. At the margin of the ulcer there is an intense inflammatory reaction.

To prove that this is so I shall first summarize what is known about ' reflux œsophagitis ', which I consider to be the best name for the lesion so ably described by Allison (1948).

In the normal person the œsophagus is completely separated from the stomach by a mechanism at, or immediately above, the œsophagogastric junction, which allows food and liquids to pass down but strictly prevents reflux. This mechanism can become inefficient under many circumstances, the most important of which are some varieties of hiatal diaphragmatic hernia and congenital short œsophagus. It may also be inefficient under conditions which appear, at first sight, to be anatomically normal. Thus Allison has shown that by placing metal clips upon the clear-cut line of demarcation between the œsophageal and gastric mucosæ at œsophagoscopy, and then screening the patients, the lower parts of the anatomical œsophagus may in fact be lined by gastric epithelium some of which lies above the ' cardiac sphincter ', and can for this reason secrete acid-pepsin into the gullet.

In some patients no harm appears to result from reflux of gastric secretions into the lower gullet, but in others an inflammatory lesion can develop in a few hours. This lesion corresponds closely to digestion of the skin of the abdominal wall around a gastric fistula. The mucosa becomes fiery, œdematous, and congested ; it bleeds easily and may be shed widely or in patches. There is leucoplakia and, in due season, erosion. At first the ulcers are shallow, involving only the mucosa, and in appearance they present as yellowish-grey patches circumscribed by a narrow crimson edge. The ulcers are generally covered by a slough, which can be swabbed away, leaving a bleeding, raw, surface. This state of subacute digestion and ulceration of the mucosa can exist, with areas of regeneration, side by side with new patches of acute necrosis, for a long time without involving the deep layers of the œsophagus, and if the patient be successfully treated complete return to normal can occur. On the other hand, if the cause persists and digestion continues, the inflammation spreads beyond the submucosa. Dense fibrous tissue forms in the musculature of the gullet and in children—as Brown Kelly (1939) and Allison (1948) have emphasized—the scar can spread up the œsophagus, producing the condition they refer to as ' ascending fibrosis '. Alternatively the inflammation may burrow through the muscle coats and beyond, so that the affected part of the gullet becomes contracted and strictured both in its longitudinal and transverse directions ; it becomes fixed, by dense fibrosis and lymphadenitis, to adjacent structures in the mediastinum.

If the affected part of such a gullet be excised and examined, certain things will be noticeable. The mucosa of the œsophagus situated above the stricture is normal. The stricture itself forms the top

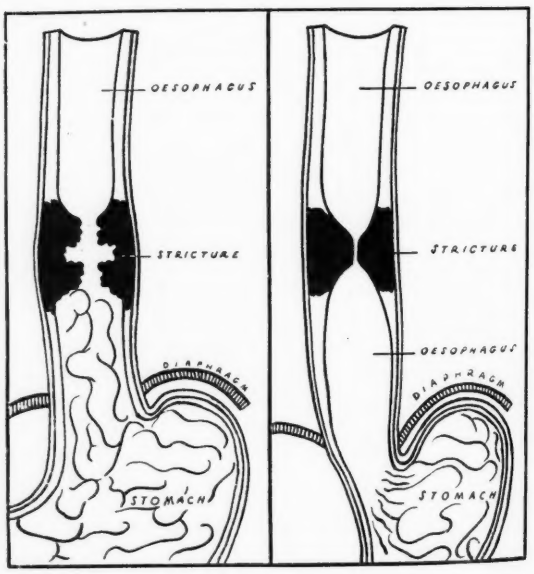

FIG. 249.—Diagram devised to stress the anatomical differences between a stricture which has drawn a pouch of stomach up into the mediastinum and one which has not.

of the abnormal zone and it is nature's way of protecting the proximal œsophagus from further excoriation. The stricture may be long or short, it is caused by scar tissue in the muscularis and the submucosa, and it often reduces the lumen to a chink. From the funnel-shaped inlet of the stricture, and extending down through it, one or more œsophageal ulcers can be seen, and although upon occasion they are found to have penetrated deeply into the muscularis, it is my experience that they

generally do not burrow through the wall of the œsophagus. Allison states that these chronic œsophageal ulcers can grow into lesions similar to gastric ulcers. Thus the features of the œsophageal ulcers, which complicate ' reflux œsophagitis ', are that they are situated in the œsophagus and are concomitant

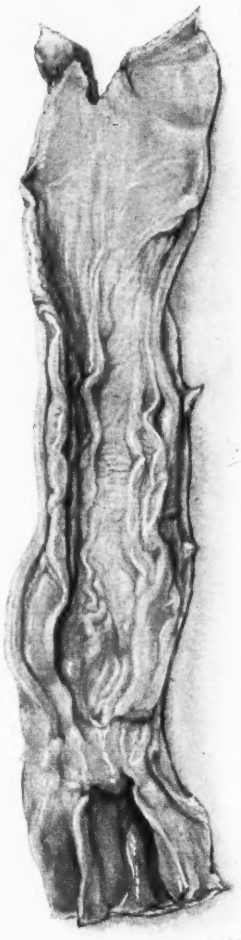

FIG. 250.—The specimen is of an œsophagus in the lower part of which is a chronic fibrous stricture which caused œsophageal obstruction. The stricture is characteristic of the type which occurs as a result of long-standing digestion of the œsophageal mucosa induced by incompetence of the cardia. There is a shallow ulcer within the lumen of the stricture itself and the chronic inflammatory process extends throughout the full thickness of the œsophagus at the level of the stricture. The gullet above the stricture is neither inflamed nor unduly dilated; it is lined by squamous epithelium. The gut below the stricture, which at first sight might be regarded as œsophagus, is a pouch of stomach, drawn up into the mediastinum by the contracting scar tissue in the stricture; it is lined by columnar epithelium. This pouch of stomach should not be described as ' ectopic '. (*This specimen and others depicted in this article were shown to me by Drs. Bratton and Bryson of the Central Histological Laboratory, Archway Hospital, London.*)

with digestion of the squamous epithelium; that they arise in an area of general acute inflammation as erosions, which can heal or persist according to the amount of gastric juice which has access to the gullet; that they remain as superficial defects for a long time in most cases, but that eventually, when the whole area has scarred up, they may burrow into or through the muscularis.

Below the stricture is a stretch of gut, which, at first sight, is apt to be taken for œsophagus, but which is generally a pouch of stomach partially enveloped by peritoneum and drawn up by scar tissue into the mediastinum. Such a pouch may be raised as high as the arch of the aorta and it is liable to be the seat of chronic gastric ulcer. It follows that these lower ulcers are gastric and not œsophageal and that they are placed below the stricture.

Careful study of the papers by Tileston, Stewart and Hartfall, and Lyall—all of whom have written about ' chronic peptic ulcer of the œsophagus '—leads me to submit two suggestions: first, that the ulcers described by these authorities are similar to each other but differ from the ulcers associated with ' reflux œsophagitis '; secondly, that there is evidence upon which to hazard a guess that none of the ulcers described in these three papers occurred in the œsophagus, but in the stomach.

To make my point I must take a stand upon two issues which are in debate :—

First, what is the œsophagus? To the anatomist it is that part of the alimentary canal which extends from the pharynx to the stomach, and the implication is that it traverses the mediastinum, whereas the stomach lies in the abdomen. It is also said to be important that the stomach is partially enveloped by a peritoneal coat.

But these criteria are not relevant to the physiologist, the surgeon, or the physician. To them the œsophagus is that part of the foregut, distal to the cricopharyngeal sphincter, which is lined by squamous epithelium; that is, the emphasis is on the nature of the secretions produced into the lumen, rather than upon the musculature or the serous covering of the walls. A piece of gullet lined by gastric mucosa, whatever the external or superficial appearances may be, functions as stomach—secreting hydrochloric acid and digestive juice—and is heir to the ailments which afflict the stomach. Now there are pathological conditions such as congenital short œsophagus in which the gastric mucosa extends far up into the mediastinum in one sheet, continuous with that lining the stomach. In such cases the segment of gut affected has generally been regarded as œsophagus, because of its position in the mediastinum and because of the absence of a serous coat. But it is stomach. Upon the normal stomach there is a bare area near to the cardia, and in cases of congenital short œsophagus—some of which may carry a partial covering of peritoneum above the crura—the bare area is larger than usual. In the remarks which follow I assume the œsophagus to be lined by squamous epithelium.

Secondly, what is meant by ' heterotopia ' and ' ectopia ' of gastric mucosa in relation to the œsophagus? I take the terms to be interchangeable and to refer to small islets of gastric epithelium found in the œsophagus and surrounded on all sides by normal squamous epithelium. I believe that most authorities concur with this definition and would not consider the terms to apply to gastric mucosa drawn up into the mediastinum, by some pathological process, but in direct continuity with that of the rest of the stomach.

I now refer again to the lesion described as chronic peptic ulcer of the œsophagus, and shall comment upon two aspects of this subject. First,

the conception that the ulcers arise in the œsophagus either in islands of ectopic gastric mucosa or as a result of secretion of acid into the gullet by such islands.

Ectopic islets were first described by F. A. Schmidt in 1805. They occur according to Schridde (1904) in 70 per cent of all the gullets he examined; they were microscopic in size and practically always

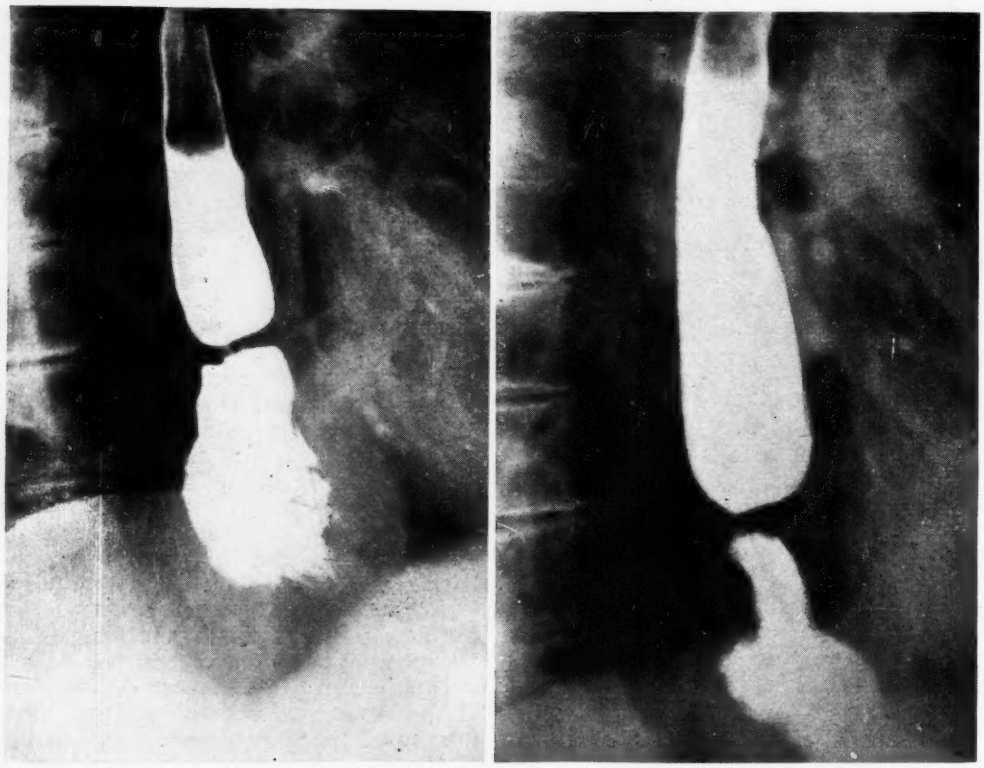

FIG. 251.—Two radiographs showing the typical appearances of a stricture caused by 'reflux œsophagitis'. In both cases the gut below the stricture, which is obviously well above the level of the diaphragm, is part of the stomach.

A

B

FIG. 252.—A, Barium swallow showing a stricture of the gullet caused by long-standing 'reflux œsophagitis', and also showing a small ulcer in the lumen of the stricture. B, Shows the same lesion photographed in the Trendelenburg position.

situated in the post-cricoid region. In 900 cases examined by Taylor (1927) of Leeds, 6 had areas sufficiently large to be visible to the naked eye and all were at the top of the gullet. They presented as small, red, depressed, and velvety patches which might be mistaken for acute ulcers. Terracol (1938) concurred that in general only the top of the gullet was affected. Rector and Connerley (1941), who worked upon infants, found 56 examples at the upper end and 2 somewhat lower down. Nobody who has studied heterotopia of gastric mucosa in the œsophagus has described a pathological lesion in an isolated islet, and thus nobody has certain evidence that ulceration has occurred in an islet; but normal islets have been found in diverticula (Jackson, 1929), in patients suffering from carcinoma (Jackson, 1925), in relation to papilloma of the œsophagus (Brooks, 1921), and in an œsophageal web (Ireland, 1933).

It is known that islets of heterotopic mucosa secrete acid, but I cannot believe that the tiny volume

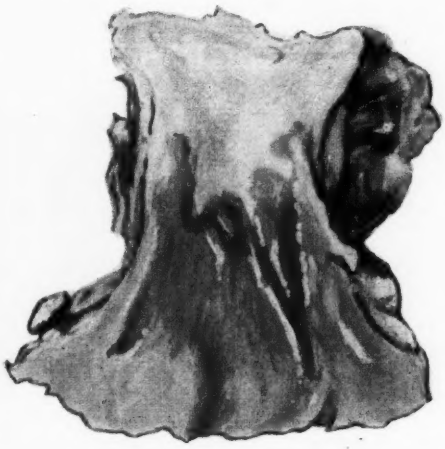

FIG. 253.—Specimen removed at operation from the patient whose barium swallow is shown in *Fig.* 252. Note the dense fibrous tissue at the top of the specimen, which represents the top of the stricture; note also that the ulcer, which shows so clearly upon the radiographs, is not much in evidence in the specimen itself. The reddened and atrophied mucous membrane below the stricture is gastric in type. This patient's trouble started ten years prior to operation, when she developed persistent vomiting during and after pregnancy. This led to a state of permanent incompetence of the cardia and hence to 'reflux œsophagitis'. As time passed the inflammation progressed to fibrous stricture and peptic ulcer in the affected area of the œsophagus. It is patients such as this who are often referred to as having a 'congenital short œsophagus'; in truth the pouch of stomach in the mediastinum has been drawn up by the scar tissue in the stricture, and the stricture is nature's way of endeavouring to protect the œsophagus from the effects of digestion by the gastric juice.

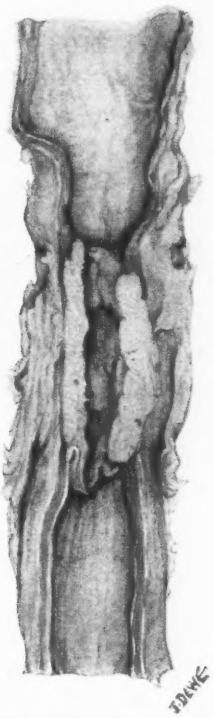

FIG. 254.—This painting is of a typical carcinoma of the œsophagus causing obstruction. It is depicted to emphasize the contrast between this type of stricture and that caused by 'reflux œsophagitis'. The mucous membrane below this squamous-cell carcinoma is squamous-cell in type—that is, the stricture has normal œsophagus proximal and distal to the lesion.

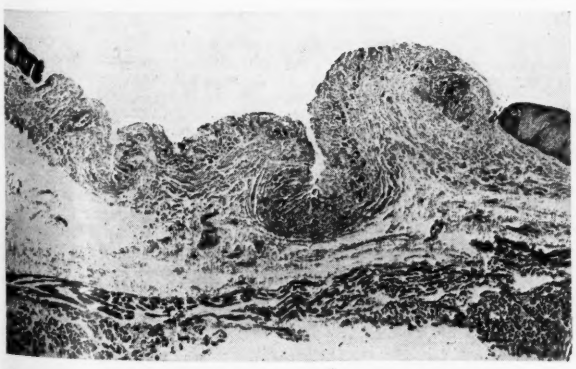

FIG. 255.—Microphotograph (low-power) showing an islet of ectopic gastric mucous membrane in the post-cricoid region of the œsophagus.

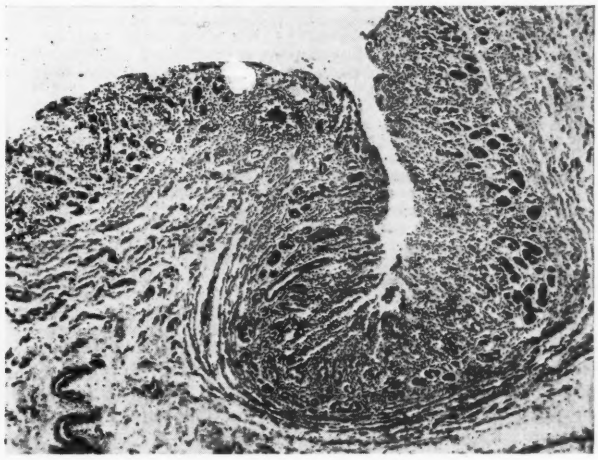

FIG. 256.—Microphotograph (high-power) of part of an islet of gastric mucous membrane from the upper part of the gullet.

of acid, diluted by pints of saliva, would be likely to harm the lower reaches of the gullet.

In short, a chronic peptic ulcer of the œsophagus has never been found in the post-cricoid region, nor has it been shown to have started in an islet of ectopic mucosa anywhere in the œsophagus. Aberrant islets hardly ever occur in the lower mediastinum, which is where the ulcers have been found.

Passing now to a comment on the actual cases of chronic peptic ulcer of the œsophagus which have been reported, and to some mounted specimens which are available for study, three papers are often quoted as authoritative—namely, that by Tileston, the second by Stewart and Hartfall, and the third by Lyall—because they leave no doubt as to the type of lesion under discussion. Each shows by photographs or drawings a number of examples of chronic peptic ulcer; the majority have perforated into some vital structure and are large, solitary excavations. These ulcers look exactly like chronic gastric ulcers, but they are stated to be in the œsophagus because they were found above the crura of the diaphragm.

I cannot prove that the ulcers did not occur in the œsophagus, but the authors cannot prove that they did, because in the 4 cases reported by Tileston personally, and in Stewart and Hartfall's case, the mucosa of the 'œsophagus' was destroyed by autolysis at the time the autopsy was performed, and, in the absence of mucous membrane there is no easy

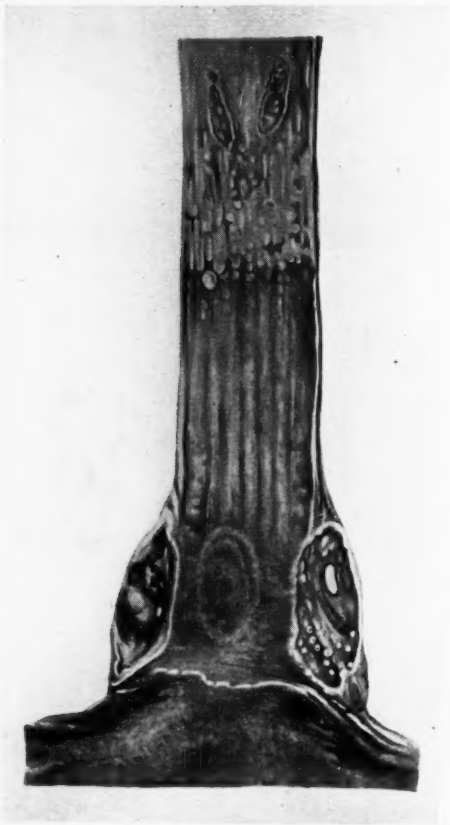

FIG. 257.—This illustration and the following legend appeared in the paper by M. J. Stewart and S. J. Hartfall upon 'chronic peptic ulcer of the œsophagus': "The œsophagus has been laid open along the middle of its posterior wall, with the result that the ulcer, situated immediately above the cardia, has been divided into two almost equal halves. In the left half, two lymph-glands, the upper of which is anthracotic, protrude from the ulcer floor. In the upper part of the right half there is a perforation which communicated with the right pleural sac. On the anterior wall at approximately the same level as the ulcer there is a well-healed oval scar. The lower three-fifths of the œsophagus has been denuded of its epithelium by peptic (post-mortem) digestion. Near the upper end two elongated patches of heterotopic gastric mucous membrane are seen." *Note*: (1) The comparison between this type of ulcer and those presented in *Figs.* 258, 259, 260 of this paper. (2) The fact that the "lower œsophagus" is denuded of epithelium and hence the difficulty of differentiating between stomach and œsophagus in this area. (3) The white line which the artist has drawn across the neck of the specimen and which purports to show the position of the cardia is probably the point at which the gastric mucous membrane stopped in this specimen. The mucosa above this point has been digested post-mortem. A normal junction of squamous and columnar epithelium at the cardia does not appear as a straight line of this type.

FIG. 258.—The specimen shows a large chronic gastric ulcer which has perforated into one of the pulmonary veins just below the level of the aortic arch. The mucous membrane in relation to this ulcer is everywhere gastric in type, and columnar epithelium extends up for a distance of 1½ in. above the top edge of the ulcer in one continuous expanse. Note that, apart from the ulcer itself, there is no evidence of superficial or deep inflammation involving the mucosa or the muscle-coats, and no sign of stricture formation. In the œsophageal mucosa above the line of junction with the stomach are two typical islets of ectopic gastric mucous membrane: these are islets of columnar epithelium surrounded by squamous mucosa of the œsophagus. The specimen is in the possession of Professor Barnard, who removed it at autopsy from a boy aged 13 who had several other congenital deformities, besides the short œsophagus, and who died from hæmorrhage. This specimen should be compared with that shown in *Fig.* 257 which it closely resembles.

way of distinguishing histologically between stomach and œsophagus. Not that the matter has been investigated in any of the cases. Lyall reported 8 cases, and in 7 he either stated specifically that the mucosa was not present o. he made no comment upon the subject, but, describing the last case, he wrote: " close examination of the mucous membrane in the region of the ulcer showed the presence of a remarkable state of affairs. The intact mucosa separating the lateral edges of the ulcer was found to be heterotopic gastric mucosa which extended as a tongue-shaped process of well-preserved tissue upwards from that of the fundus of the stomach. . . . The mucosa bore a resemblance to that normally found towards the pyloric end of the stomach ". In this quotation Lyall has described, as I see it, a chronic gastric ulcer occurring in a pouch of mediastinal stomach, but he has assumed it to be œsophagus and called the columnar mucosa ' heterotopic '. In most of the specimens described by these authorities the gastric mucosa is said to stop short at the place where the cardiac sphincter is assumed to have been, and above this the walls of the gullet are denuded of epithelium for a greater or lesser distance. This line, defining the supposed upper limit of the gastric mucosa, is depicted as a straight transverse ridge in drawings and photographs, and from my studies I believe that it is not the line of junction between the stomach and œsophagus. The anatomical junction between the two epithelia is not normally a straight horizontal line. My explanation of the line shown in the drawing is that it represents the level of the crura of the diaphragm which have partially occluded the œsophagus after death and so caused secretions to stagnate and accumulate above.

FIG. 259.—This drawing was made from a specimen in which there is a chronic gastric ulcer situated in the lower part of the specimen. The ulcer was found in the mediastinum above the level of the crura of the diaphragm, but the mucous membrane by which it is surrounded is gastric on all sides. It will be seen that small pieces of tissue have been removed for microscopy, one through the ulcer itself and another about 2½ in. higher up, and these confirm that this ulcer is situated in the stomach. The mucosa at the top of the specimen is œsophageal, and thus the case is one showing a congenital short œsophagus with a stomach extending high up into the mediastinum and containing a chronic gastric ulcer. Note the absence of any suggestion of stricture formation and compare this condition with that depicted in *Fig.* 250, namely, " reflux œsophagitis with chronic œsophageal ulcer and stricture formation ".

FIG. 260.—The specimen, which has been painted, shows a typical chronic gastric ulcer in a stomach which extends high up into the mediastinum. From the shape of the specimen it will be apparent that the ulcer lay above the part which upon external examination appeared to be the cardia. In fact, the junction of gastric and œsophageal mucosa is at the top of the specimen. Note also that there are several acute gastric erosions in relation to the chronic ulcer and that the rugæ in the gastric mucosa above the ulcer do not conform in pattern with those found typically in the stomach: for this reason a radiologist cannot always distinguish accurately between œsophagus and stomach. There is no general inflammation of the parts, either above or below the ulcer, and no suggestion of stricture formation. The slight difference in the colour of the gastric mucosa in the upper and lower parts of the specimen is accounted for by partial post-mortem digestion in the former, and the line of demarcation between the two—which others have assumed to be the junction of columnar and squamous epithelia—is probably caused by the retention of gastric secretions above the diaphragmatic pinch-cock after death.

Turning from negative to positive evidence, a striking feature of these cases is that the typical symptoms and signs of ' reflux œsophagitis ' have generally not been present nor have the ulcers often produced fibrotic stenosis of the gullet. On the contrary, the patients have come to hospital because of emergencies such as massive bleeding, perforation, or carcinoma. They have died and typical gastric ulcers have been found at autopsy.

My views seemed to me to be confirmed when I was shown a specimen (*Fig.* 258) by Professor Barnard. His patient was a child, aged 13, who had several other congenital deformities, and who died from perforation of a chronic ulcer into a large pulmonary vein. The specimen is similar in many ways to that depicted by Stewart and Hartfall. There are two small islets of ectopic mucosa at the top of the gullet and below these the œsophageal mucosa stops short. Below the level of the arch of the aorta the mucosa is everywhere histologically gastric in type and the chronic ulcer which has perforated into one of the great vessels is a stomach ulcer. The original lesion was a congenital short œsophagus, and there is no suggestion of diffuse œsophageal fibrosis or of stricture.

I have also had the advantage of examining other specimens with Dr. Bratton at Archway Hospital. Some of these had typical gastric ulcers, and it had been assumed that because, upon microscopy, the mucosa around these ulcers was gastric in type that the lesions had occurred in islets of ectopic gastric mucosa. In fact, the ulcers were gastric ulcers in mediastinal extensions of the stomach, and the patients had congenital short gullets.

In conclusion, I stress that the word 'œsophagitis' is now a blunderbuss term used to cover many different pathological lesions; it should always be qualified by a descriptive adjective such as '*reflux* œsophagitis'. I believe that reflux œsophagitis is common and that it can give rise to ulceration of the œsophagus and stricture formation. In contrast with this lesion is another which has always up till now been assumed to be identical with it, and which has generally been described by pathologists—as opposed to clinicians—under the heading of 'peptic ulcer of the œsophagus'. I submit that most of these cases are in truth examples of congenital short œsophagus, in which there is neither general inflammation nor stricture formation, but in which a part of the stomach extends upwards into the mediastinum—or even to the neck—and that in this stomach a typical chronic gastric ulcer can form. I urge that, as accurate surgery must rest upon accurate pathology, we must distinguish between gastric and œsophageal ulcers.

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CROHN'S DISEASE

A SURVEY OF THE LITERATURE AND A REPORT ON 34 CASES

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HISTORICAL

FOUR contributions are outstanding in the history of this condition: (1) Coombe and Saunders (1806)—earliest recorded description. (2) Dalziel (1913)—description of 8 cases; recognition that the condition was not tuberculous. (3) Crohn, Ginzburg, and Oppenheimer (1932)—description of clinical and pathological features. (4) Hadfield (1939)—description of specific histological appearances.

1. In 1806, Dr. William Saunders read, at the Royal College of Physicians in London, a description of "A singular case of stricture and thickening of the ileum", in which "the lower part of the ileum as far as the colon was contracted for the space of 3 feet to the size of a turkey's quill". There were also lesions in the colon.

Abercrombie in 1828 described two similar cases. Moynihan (1907) and Mayo Robson (1908) both discussed inflammatory tumours of the large bowel.

2. In 1913, Dalziel read a paper on "Chronic Interstitial Enteritis" at the Annual B.M.A. Conference at Brighton. He described 8 cases, with a detailed account of the pathology; an attempt had been made to find a causative organism, but had revealed only *B. coli* in one case. There was no evidence of tuberculosis. He concluded—"As far as I am aware the disease has not been previously described, but it seems probable that many cases must have been seen and have been diagnosed as tuberculous."

3. In 1932, Crohn, Ginzburg, and Oppenheimer, of the Mount Sinai Hospital, New York, described

the disease of the terminal ileum to which they gave the name ' regional ileitis ', and immediately drew world-wide attention to the subject. It became known alternatively as Crohn's disease. Their description of the clinical and pathological aspects was so complete that little material knowledge has since been added to it. Nevertheless, much has been written on the subject, particularly in America, and a paper written by Warren and Somers in 1948 ends with a bibliography containing some 200 references.

Crohn originally believed that the lesions occurring in the terminal ileum were an entity distinct from the granulomata known to occur in the large intestine, but later (1936) broadened his conception and described 9 cases of combined ileitis and colitis.

4. Hadfield, in 1939, after a careful study of the early lesions of the disease, described certain histological features which he regarded as being specific, and peculiar to Crohn's disease. Further reference is made to this below.

PATHOLOGY

(*Figs.* 261–267)

Site of Lesions.—The terminal ileum was affected in 30 (88 per cent) of cases in this series. In 13 (38 per cent) the colon was involved, but in only 2 of these was the lesion isolated, and in every case involved the right side of the colon. Hadfield (1949, b) gives it as his impression that in isolated colonic lesions it is the transverse colon that is most often affected. In only 1 of our cases was the jejunum involved (3 per cent). Warren and Somers (1948) report an incidence of 9 per cent in the jejunum.

The ileal lesion usually extends right up to the ileocæcal valve, and averages 10 in. in length, though much longer segments may be affected. Crohn (1934) reports a case in which the whole of the ileum and a part of the jejunum were involved, while in one of Dalziel's cases the entire small bowel was affected. Occasionally there are ' skip ' areas, with healthy bowel intervening; this was the case in 15 per cent of the present series. However, multiplicity is a feature more characteristic of tuberculous than of ' non-specific ' ileitis.

There are no convincing reports of the occurrence of the disease in the œsophagus, stomach, or duodenum.

Initial Lesion.—There is not yet any certainty as to what constitutes the early phase of the disease. Some authors speak of an acute regional ileitis, others describe an acute ulcerative phase. Crohn was inclined to believe that ulceration was the initial lesion. An ' acute terminal ileitis ' is periodically encountered during operations for supposed acute appendicitis—is this to be regarded as an early form of the disease? At least 26 such cases have been encountered in this way at the General Infirmary at Leeds in the last fifteen years. A variable length of terminal ileum is acutely hyperæmic and œdematous, and may show subserous petechial hæmorrhages, the mesenteric glands are usually acutely inflamed, and there may be some free fluid. Sometimes the appendix is also involved in the process. Ten of these cases have been followed up: no evidence of persistence of symptoms or recurrence has been found, although no treatment has been carried out other than exploration and sometimes appendicectomy. It seems very unlikely that Crohn's disease begins in this way, more likely that the process is insidious from the start, and that when the onset is sudden and the history short, secondary infection has attacked a segment of bowel already the seat of chronic disease.

Developed Lesion.—Characteristically the whole circumference of the terminal ileum presents a turgid and congested appearance, the wall is thickened and rigid, it has a rubbery feel, and has been likened to a garden hose-pipe (*Fig.* 261). The thickening may

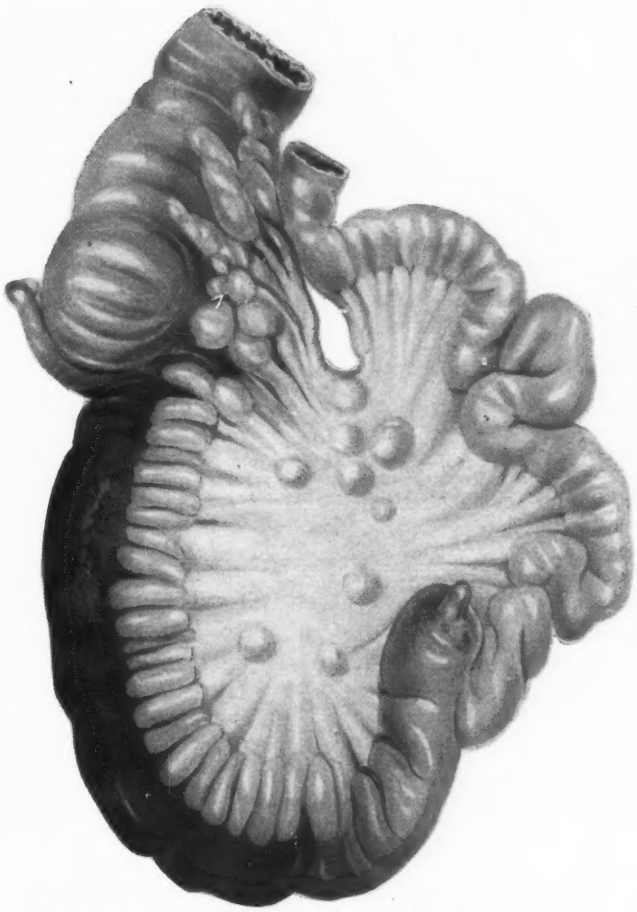

FIG. 261.—*Case* 8 (A/61/1939). Miss C. W., aged 21. Hemicolectomy right (G. A.) 1939. Typical ' hose-pipe ' type of lesion in terminal ileum with excessive mesenteric fat and enlarged glands. Note Meckel's diverticulum.

extend into the adjacent mesentery (*Fig.* 265) the leaves of which may appear fibrosed and contain an excess of fat. The regional lymph-nodes are pink, enlarged, and fleshy. Small whitish ' tubercles ' are commonly seen on the serous surface of the affected segment (*Figs.* 263, 266); these closely resemble to the naked eye the true tubercle of Koch's infection—one of the reasons perhaps why the condition was so long thought to be tuberculous.

The transition from diseased to healthy bowel is usually abrupt (*Fig.* 262) and clearly demarcated on the surface, though the mucosal changes may extend beyond.

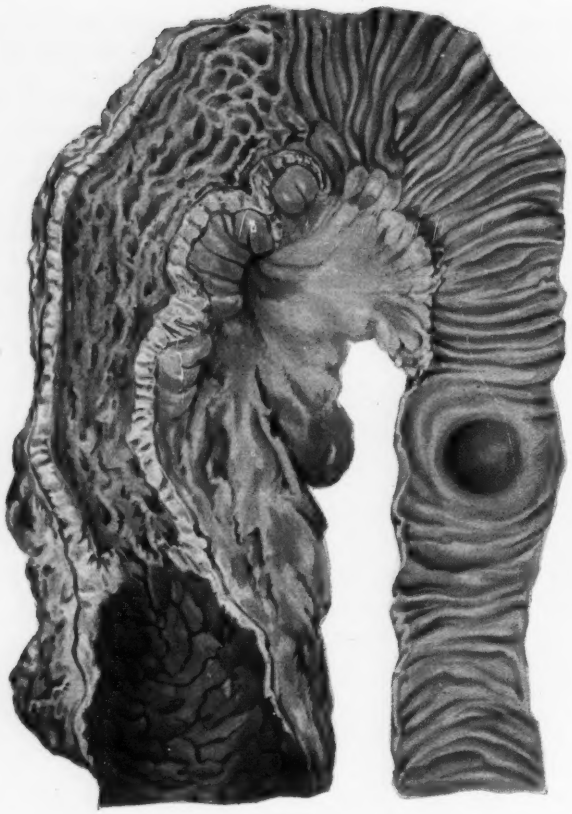

FIG. 262.—*Case* 8 (A/61/1939). Specimen opened to show œdematous ulcerated mucosa and thickening of ileal wall. Note Meckel's diverticulum.

FIG. 263.—*Case* 28 (A/171/47). K. B., aged 25. Hemicolectomy right (G. A.) 1947. Terminal ileum showing 'tubercles' or granular appearance.

FIG. 264.—*Case* 28 (A/171/47). Specimen showing involvement of the posterior aspect of the cæcum.

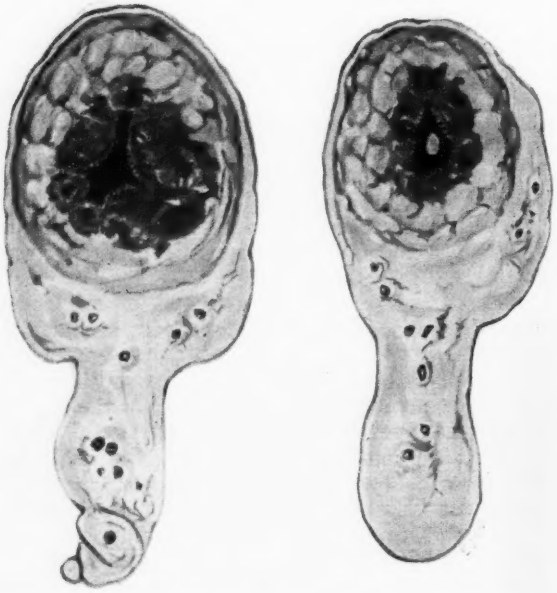

FIG. 265.—*Case* 28 (A/171/1947). Cross-section showing gross mesenteric thickening.

When the colon is affected, the appearance is rather different. The thickening and induration are less regular and may not affect the whole circumference of the bowel, so that if a lesion is placed posteriorly in the cæcum or ascending colon it may easily escape notice (*Figs.* 263, 264).

The mucosal lesion is variable. Ulceration is usually present, sometimes very extensive; sometimes occasionally it is absent. The ulcers tend to be shallow, to be more numerous on the mesenteric border, and to be oval in an axial direction. The submucosa is much thickened, distorting or obliterating the normal mucosal folds, sometimes producing a coarsely mamillated or 'cobblestone' appearance (*Fig.* 267). This thickening in the submucosa, combined with fibrosis in the muscular layers, produces a narrowing of the intestinal lumen, compensatory

muscular hypertrophy in the bowel above, and in a late stage complete obstruction, usually assisted by the impaction of some particle of undigested food.

FIG. 266.—*Case* 25 (A/1077/1942). Mrs. B. R., aged 28. Hemicolectomy right (G. A.), 1942. Terminal ileum, again showing granular appearance and large fleshy mesenteric gland.

HISTOLOGY

(*Figs.* 268–271)

According to Hadfield (1939) the earliest histological change is an endothelial-cell proliferation in the submucous lymph-follicles, which enlarge up to 3 mm. in diameter (*Fig.* 271). At a relatively early stage giant cells appear in their centres. Hadfield speaks of these giant-cell systems as specific and regards the appearance as peculiar to Crohn's disease. They may closely resemble tubercle follicles and

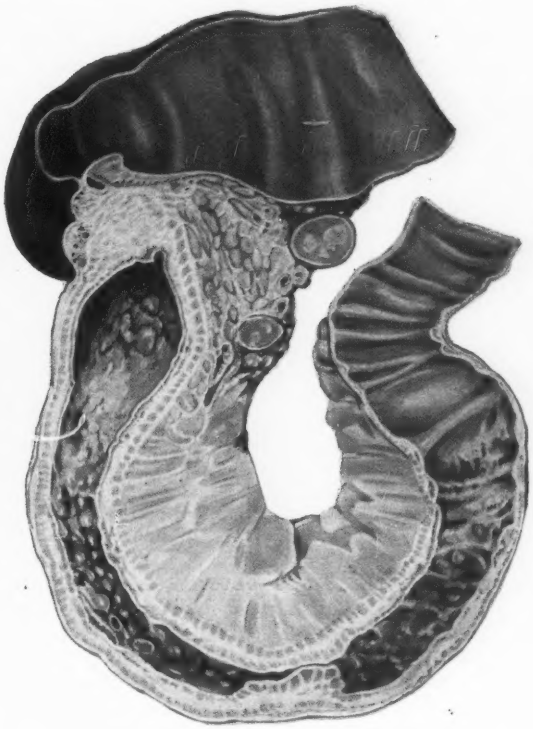

FIG. 267.—*Case* 25 (A/1077/1942). Section to show gross stenosis, 'cobblestone' appearance of ileal mucosa, and enlarged lymphatic glands.

have been called 'pseudo-tubercles'. However, they show no tendency to caseate, and acid-fast bacilli are not found in them. Accompanying this change, and probably secondary to lymphatic obstruction produced by it, there is a considerable degree of lymphatic œdema. At this stage the surface of the mucosa shows relatively little ulceration. Identical giant-cell systems may be seen in the regional lymph-glands.

In the intermediate stages the hyperplastic follicles undergo retrogression, but increasing stenosis has

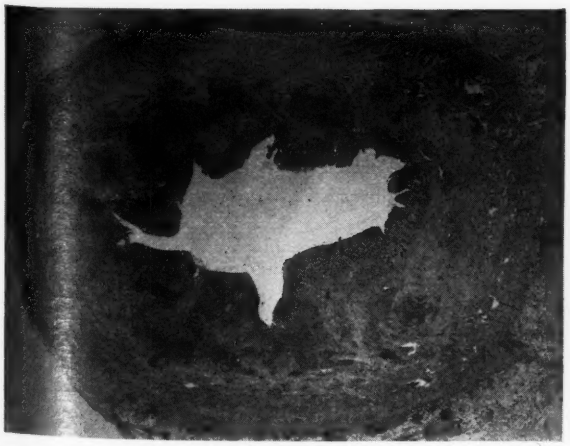

FIG. 268.—*Case* 28. Ileum cross-section, showing submucous thickening, lymphocytic infiltration, with endothelioid follicles.

FIG. 269.—*Case* 28. Cæcum cross-section, showing similar appearances, but submucous thickening affects about half the circumference of the bowel.

usually given rise to increasing ulceration (*Fig.* 270), and secondary intramural infection destroys the specific lympho-reticular hyperplasia characteristic of the earlier lesions. All layers are crowded with lymphocytes, plasma cells, and eosinophils.

FIG. 270.—*Case* 28 (A/171/1947). Ileum (low-power), showing ulceration on the left and flattened atrophic epithelium on the right. Submucous fibrosis is also well shown.

In the late stages there may be marked fibrosis (*Fig.* 270) and the formation of intramural abscesses leading to adhesion to other viscera, perforation with fistula or local abscess formation, or rarely free perforation into the general peritoneal cavity. These internal fistulous communications are most common between ileum and cæcum or ascending colon; they are also relatively common between ileum and sigmoid, or ileum and ileum; much less common is an ileovesical fistula. Fistulæ communicating with the exterior are usually the result of the drainage of an abscess or the removal of an appendix, but in the present series spontaneous fistulæ with the vagina and the umbilicus have occurred.

In those cases coming to autopsy, lesions outside the bowel and mesentery have been encountered only once, in a case in which Warren and Somers (1948) reported finding a small granuloma in the liver.

Until recently Hadfield had not been able to satisfy himself that the disease attacked the colon primarily, but has now seen (1949, b) 3 specimens in which the classical submucous endothelial hyperplasia with non-caseating giant-cell systems was present.

CLINICAL FEATURES

(*Tables I, II*)

Age and Sex Incidence.—Young adults are most commonly affected; in this series the average age was 31, the youngest was 14, and the oldest 69. A well-documented case with post-mortem findings has been reported in a newborn infant by Koop, Perlingiero, and Weiss (1947) in which the process was presumed to have begun *in utero*. The mother was perfectly healthy. Other cases in infancy and childhood have been reported (Ebrill, 1945).

The sex incidence is variously reported and is therefore probably equal. Crohn originally described a male preponderance of 2 to 1; in the present series exactly the reverse ratio existed.

Predisposing Factors.—Some writers have found that the disease has a predilection for the Jewish race, others have not confirmed this. About a tenth of the population of Leeds is Jewish, yet only 1 of our 34 cases was known to be of this extraction.

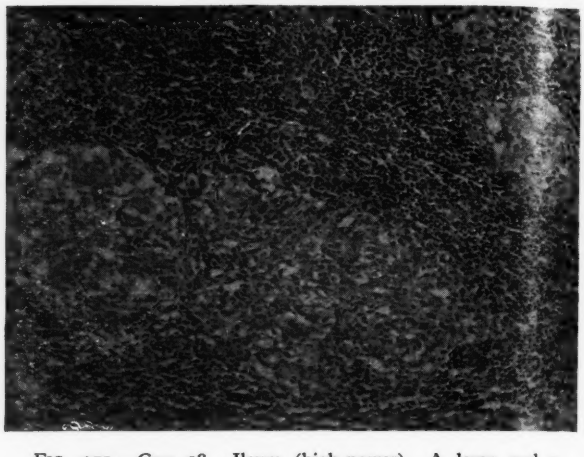

FIG. 271.—*Case* 28. Ileum (high-power). A large and a smaller endothelioid follicle with occasional giant cells.

Bockus (1945) considers that climate plays a part and reports that the disease is relatively rare in southern U.S.A., Central America, and the northern part of South America.

Table I.—ANALYSIS OF 34 CASES

(*Leeds General Infirmary*)

Sex distribution { F. 24 / M. 10

Age { Average 31 / Youngest 14 / Oldest 69

	Cases	*Per Cent*	
Operated on as acute	16	47	
Pain	34	100	
Diarrhœa	25	73	
Constipation	8	23·5	
Loss of weight	19	55	
Lump in right iliac fossa	13	38	
Previous appendicectomy	9	26	
X-ray diagnostic—			
All cases	12	35	
Non-acute	9/15	60	
Associated fistula	6	18	
Internal	4	12	
External	4	12	
Internal and external	2	6	
Lesion—			
Single	25	73	
Multiple (i.e., 'skip areas')	5	15	
Jejunum	1	3	
Ileum	30	88	
Colon	13	38	
(Isolated)	3	9	
Resection in 1 stage	22	64	
Resection in 2 stages	5	15	
Short-circuit (simple)	3	9	
Short-circuit (exclusion)	1	3	
Post-operative deaths	6	18	
Recurrence, in survivors traced	4/22	18	32 per cent—unsatisfactory results
Symptoms but recurrence unproved	3/22	14	

Average recurrence interval, 5 years 5 months (longest 12½ years)

There seems to be a certain temperament or personality pattern that is found rather regularly in this disease. This is referred to again below.

A number of cases with a familial incidence have been reported, with sufficient frequency perhaps to

be of significance in a relatively rare disease. There was 1 such instance in this series.

Clinical Course.—Crohn and others (1932) described 4 types of clinical course under which most of the cases might be grouped: (1) Acute intra-abdominal disease with peritoneal irritation; (2) Symptoms of ulcerative enteritis; (3) Symptoms of chronic small-bowel obstruction; (4) Persistent and intractable fistulæ.

1. *Acute Intra-abdominal Disease with Peritoneal Irritation* (29 per cent).—This was the mode of presentation in 10 (29 per cent) of this series, who were operated upon as emergencies without preliminary investigation, usually with a presumptive diagnosis of acute appendicitis. (We have excluded from this group that form of acute ileitis which has been referred to above.) In the majority of these cases a resection, sometimes a short-circuit, was performed for a lesion which was obviously of long standing.

In most of these cases, while the acute and severe symptoms were of short duration, there was a history, dating back months and perhaps years, of occasional vague abdominal discomfort, colicky pain, or looseness of the stools.

The acute syndrome, almost indistinguishable from appendicitis, consisted typically of low fever, colic, vomiting, and pain and tenderness in the right iliac fossa, with sometimes a palpable lump and diarrhœa. It is the diarrhœa and the past history in these cases which are warnings to the surgeon to make an exploratory incision.

It has often been remarked that the acute onset is related to an acute upper respiratory infection or an attack of tonsilitis. It can well be imagined that an ileum the seat of chronic œdema and lymphatic stasis is like tinder, waiting to be set alight by any stray spark of bacterial infection that may reach it from the blood-stream or intestinal lumen.

2. *Symptoms of Ulcerative Enteritis* (29 per cent).—In this group diarrhœa is the prominent feature, though pain, often relieved by bowel movement, was always present in our cases. Loss of weight and anæmia are usual, with occasional bouts of low-grade fever.

Blood, whether occult or overt, may usually be found in the stools.

In some of our cases in this group a diagnosis of ulcerative colitis had originally been entertained.

This is the group in which internal fistulæ are most likely to be found, and in which the prognosis is most serious. Two of our fatal cases in this group had fistulæ between the ileum and the sigmoid.

3. *Stenotic Group* (32 per cent).—In these cases pain is to the fore—periodic, cramp-like abdominal colic often associated with sensations of rumbling, and the feeling of a lump that comes and goes, with occasional nausea. Bowel action may be little altered, or there may be periods of constipation or of looseness, or both. These symptoms are in many cases not very severe, and may persist for a long time without producing any loss of weight or obvious ill health. The patient is anxious about his symptoms; the doctor, often unable to find any cause for them, treats them symptomatically, suspecting, perhaps correctly, that the patient is neurotic. Under these circumstances, additional anxiety symptoms are likely to develop, further clouding the issue.

Sometimes the issue is cleared, as happened for example in one case by the impaction of an undigested pea, and the onset of acute intestinal obstruction.

Short of this, a careful examination may reveal tenderness and perhaps a lump in the right iliac fossa, and in a thin subject visible peristalsis may be seen.

A barium meal and follow-through examination should reveal the presence and site of the stricture.

4. *Persistent and Intractable Fistulæ* (9 per cent).—It is well known that persistent fistulæ after appendicitis or drainage of an abscess are commonly a manifestation of Crohn's disease. This was the case in 3 (10 per cent) of this series. It is less well known that there is an association between Crohn's disease and fistula-in-ano. Out of 114 cases reported by Jackman and Smith (1943) 8 sought medical treatment primarily because of anal fistula. No anal fistulæ were encountered in this series.

Spontaneous external fistulæ, not precipitated by operative interference, are decidedly rare. This series contains 2 examples, one occurring through the umbilicus, the other, perhaps not a true external fistula, through the vagina.

This division of the disease into separate and distinct clinical types is naturally rather artificial; not all cases can be so classified, and some pass from one group into another. The majority of cases do, however, fit into one or other of these categories, and the classification is useful.

Symptomatology.—

1. *Pain.*—Has been present in every case, and in the majority is the leading symptom. Usually it is a characteristic, centrally placed, small-bowel colic. In some, the onset is related to the taking of food, and occasionally the pain has been referred to the epigastrium, and the simulation of ulcer pain has been very close.

2. *Diarrhœa.*—Present in about 70 per cent of all cases, it amounts in many to little more than looseness of the stools, but in some was prolonged and debilitating. In one case, originally diagnosed as ulcerative colitis, severe hæmorrhage was also a feature—a fistula between the sigmoid and the ileum was present in this case.

3. *Loss of Weight.*—This occurred in rather under half the cases, but in a few was extreme.

4. *Palpable Mass.*—Thirteen cases (38 per cent) had a palpable mass in the right iliac region, of variable tenderness, depending upon the acuteness of the condition.

In the acute cases a mass was absent more often than it was present. In half the non-acute cases, it was present. No doubt it would have been recorded more frequently in the acute cases had its presence not been obscured by guarding or rigidity.

5. *Duration of History* (*Table III*).—In the majority of cases the history is measured in years rather than in months. In only 4 out of 34 cases was the duration of symptoms less than a month, and in only 2 less than a week.

Rarer Manifestations in the Series.—

1. *Spontaneous Vaginal and Umbilical Fistulæ* have already been referred to.

2. *Acute Ileal Perforation* in a patient while in hospital under investigation for 'dyspepsia' of ten years' duration. This was unfortunately fatal, and

Table II.—More Detailed Analysis of

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Sex	F.	F.	M.	M.	F.	M.	F.	F.	F.	F.	M.	F.	F.	F.	F.
Age	23	40	18	36	40	23	41	21	32	38	27	49	15	23	29
Duration of history	6/12	2	3/12	10	4/12	1/52	8/12	4/12	6/12	1/52	6	1/12	2/52	7	2
Acute operation	x	x	—	x	x	x	x	x	—	x	x	x	x	x	—
Pain	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Diarrhœa	x	x	—	x	—	—	x	x	x	x	x	—	—	—	x
Constipation	—	—	—	x	x	x	x	—	—	—	—	x	—	—	—
Loss of weight	—	x	x	—	—	—	x	x	x	—	x	x	—	x	?
Lump in right iliac fossa	—	x	x	x	?	—	—	—	x	x	—	x	x	—	x
Previous appendicectomy	x	—	—	—	—	—	—	x	x	—	—	—	—	—	x
X-ray diagnosis	—	—	x	—	—	—	—	x	x	—	x	—	—	—	—
Associated fistula :	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
a. internal															
b. abdominal															
c. anal															
Lesion : single	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
multiple	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
in jejunum	—	—	—	—	—	—	—	—	x	—	—	—	—	—	—
in ileum	x	x	x	x	—	x	x	x	—	x	x	x	—	x	x
in colon	—	—	x	x	x	—	—	—	—	—	—	—	x	—	—
Resection in : 1 stage	x	x	x	x	x	—	—	x	x	x	—	—	Appy.	x	x
2 stages	—	—	—	—	—	—	x	—	—	—	—	x	—	—	—
Short-circuit	—	—	—	—	—	x	—	—	—	—	x	—	—	—	—
Short-circuit exclusion	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
D. post-operation	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Recurrence	U.T.	—	—	U.T.	U.T.	—	S.	x	x	—	—	d.	U.T.	—	—
Years since operation or between operation and symptoms of recurrence	—	8 7/12	8 2/12	—	—	13 2/12	10 3/12	12½	4	5½	5 9/12	—	—	5	4 4/12

U.T. Untraced. D. Died from Crohn's disease. d. Died from other

at post-mortem a typical obstructing Crohn lesion was found 1 ft. above the ileocæcal valve with a sloughing ulcer above the constriction.

3. *Recurrent Mesenteric Mass without Intestinal Lesion.*—Nine years after hemicolectomy for Crohn's disease, the patient complained of backache and was found to have a large mass in the right side of the abdomen. At laparotomy, tumour was found to be a retroperitoneal glandular mass fixed to the posterior abdominal wall. The bowel was carefully examined, but no abnormality was found and the anastomosis appeared healthy. No attempt was made to remove the mass. A biopsy showed a portion of chronic inflammatory tissue. The wound was closed, with a stab drain in case of bleeding from the numerous adhesions which had been divided—perhaps inadvisedly, because, two years later, it has still not healed, and discharges a little clear fluid. The mass is reduced in size, and she herself is well. This patient was treated with calciferol (*see below*).

Table III.—Duration of History

1 week or less	2
1 week to 1 month	2
1 to 6 months	7
6 months to 2 years	8
2 to 10 years	9
Over 10 years	5
Unrecorded	1
Total	34

This type of recurrence, apparently confined to glandular and mesenteric tissue, is most unusual.

4. *Familial Incidence.*—Cases with clear familial incidence have been reported from time to time, and it seems worth while emphasizing that this series contains one example. Our patient, a woman of 29, has had trouble since 1937; she had had an appendicectomy at another hospital, and has since then had six operations at various hospitals for drainage of abscesses and closure of fistulæ; a resection has not been attempted on her as yet. Her brother was more fortunate (he has only had two operations, the second of which was a resection at the Charing Cross Hospital) and is now well. Both patients are of similar temperament, both "suffer from nerves" (he is an actor). They have both lived in different cities for many years.

5. *Lesion confined to Appendix.*—One case which was thought at operation to be an appendix abscess was treated by appendicectomy and drainage. The appendix aroused some suspicion and was histologized. The report was—"Appendix infiltrated with endothelial and giant cells. Typical Crohn lesion as far as the base of the appendix". The wound healed, and the patient has remained well for six years.

SPECIAL INVESTIGATIONS

1. Blood Examination.—Is not helpful from the point of view of diagnosis. A moderate leucocytosis was present in about two-thirds of the cases, but its absence is of no significance. There is a tendency towards anæmia in most cases; in a few this was severe and necessitated transfusion. Bockus (1945) states that severe anæmia is almost always associated with plasma-protein deficiency.

2. Stool Examination for Occult Blood.—This is often present, and is valuable evidence of ulceration.

3. Mantoux Reaction.—Is inconclusive (Blackburn, Hadfield, and Hunt, 1939).

4. X-ray Examination of Alimentary Tract (*Fig.* 272).—The results are highly reliable. In 35 per cent of this series (i.e., 50 per cent of the non-acute cases) a pre-operative diagnosis was made by this means. In no case in which a barium meal and follow-through examination were made did the radiologist fail to demonstrate a lesion, and usually indicated its exact nature.

Kantor's 'string sign' is well known (1934). The terminal portion of ileum presents a long, irregular narrowing, so that in an advanced case the normal

34 CASES OF CROHN'S DISEASE (*see Table I*)

16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	TOTALS
F.	F.	F.	M.	M.	F.	M.	M.	F.	F.	F.	F.	M.	F.	F.	F.	F.	M.	F.	F. 24, M. 10
56	30	14	35	36	69	46	33	25	28	38	68	25	26	29	29	27	37	22	Average 31
4/12	7/12	4	10	7/12	10	12	6/52	?	1	16	1	5	19	12	1½	2	20	6	
—	—	—	—	—	—	—	×	—	—	—	×	×	—	—	—	×	—	—	16 (47 per cent)
×	×	×	×	×	×	×	×	?	×	×	×	×	×	×	×	×	×	×	34 (100 ,,)
×	×	×	×	—	—	×	×	?	×	×	×	×	×	×	×	×	×	×	25 (73 ,,)
—	—	—	—	—	—	—	—	?	—	×	×	×	—	—	—	—	—	—	8 (23·5 ,,)
×	×	×	×	—	×	—	—	?	?	—	—	—	×	×	×	—	×	×	18 (53 ,,)
?	?	—	?	—	×	—	—	?	×	×	×	—	—	—	—	—	×	—	13 (38 ,,)
×	×	—	—	—	—	—	—	?	—	—	—	—	—	×	×	—	×	—	9 (26 ,,)
—	×	×	—	—	—	×	—	×	×	—	×	—	—	×	—	—	×	—	12 (35 ,,)
—	×	×	×	—	—	—	—	—	—	×	—	—	—	×	×	—	—	—	6 (18 ,,)
	×	×	×							×				—	—				4 (12 ,,)
	×	×	—							—				×	×				4 (12 ,,)
	—	—	—							—				—	—				0
×	—	×	—	×	×	×	×	×	—	×	×	—	—	—	×	—	×	—	25 (73 ,,)
—	×	—	×	—	—	—	—	—	×	—	—	×	×	—	—	—	—	—	5 (15 ,,)
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1 (3 ,,)
×	×	—	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	30 (88 ,,)
—	×	×	×	—	—	—	—	—	—	×	×	×	×	×	—	—	—	×	13 (38 ,,)
×	×	—	×	×	—	×	×	×	×	×	—	×	—	—	—	×	—	—	22 (64 ,,)
—	—	×	—	—	—	—	—	—	—	—	×	—	—	—	—	—	×	×	6 (18 ,,)
—	—	—	—	—	—	—	—	—	—	—	—	—	—	?	×	—	—	—	3 (9 ,,)
—	—	—	—	—	—	—	—	—	—	—	—	—	×	—	—	—	—	—	1 (3 ,,)
—	×	×	×	—	×	—	—	—	—	—	—	—	—	—	×	—	—	×	6 (18 ,,)
—	D.	D.	D.	—	D.	—	—	—	U.T.	×	—	S.	—	?	D.	S.?	×	D.	
4/12				3½		1 5/12	10/12	6/12		5	6/12	2	2/12			2 10/12	1/12		

causes. S. Symptoms present, but recurrence not confirmed.

ileum above seems to be connected to the cæcum by a piece of string. In addition, there is ileal stasis, and dilatation above the lesion, depending upon the degree of stenosis. Sometimes the appearance of a double string is seen, when in addition there is a fistulous track connecting ileum with cæcum.

FIG. 272.—Radiograph showing: (1) Narrowed terminal ileum; (2) Fistulous track between ileum and abdominal wall; (3) Cæcal spasm; (4) Dilated proximal ileum; (5) 'Emptiness' due to inflammatory mass; (6) Spasm of transverse colon in neighbourhood of inflammatory mass. (*Case* 31.)

The presence of an inflammatory mass in the ileocæcal region is shown in the barium follow-through series by an appearance of 'emptiness', due to absence of small intestine and elevation of the cæcum.

Fistulæ connecting with the colon produce deformity in the colon by the spread of stenosing inflammation around it, and may with a barium enema closely resemble carcinoma. Deformity in the cæcum may also be produced by spasm alone (Stierlin's sign).

DIFFERENTIAL DIAGNOSIS

1. Hyperplastic Ileocæcal Tuberculosis.—This is a purely histological and bacteriological differentiation, and cannot be made clinically or on naked-eye appearances. Calcified mesenteric glands should not be taken as evidence that the intestinal lesion is tuberculous. Hyperplastic intestinal tuberculosis is classically not associated with tuberculosis elsewhere.

2. Ulcerative Intestinal Tuberculosis.—In the healing stages produces multiple annular constrictions, not showing the same predilection for the terminal ileum. It is usually associated with an active pulmonary lesion.

3. Actinomycosis.—Actinomycosis has to be considered in a case of persistent fistula after appendicectomy. Culture may be necessary to demonstrate the fungus, and may have to be repeated. Actinomycosis has a tendency to invade the psoas muscle and produce spasm.

4. Other Conditions.—Those to be considered are ulcerative colitis, carcinoma, Hodgkin's disease, lymphosarcoma, and talc granuloma.

TREATMENT

In their original paper Crohn and others (1932) reported that after resection 13 out of 14 cases were

restored to complete health. Resection is still advocated by most authors as the treatment of choice.

Discussing the relative merits of one- and two-stage resection, Mayo and Judd (1941) reported experience with 100 cases as follows :—

	No. of Cases	*Mortality (per cent)*
One-stage resection	32	22
Two-stage resection	64	3

They therefore recommended resection in two stages.

Garlock and Crohn (1945), reviewing 164 cases, remarked that in 25 instances in which they had performed a two-stage resection, the specimen when finally removed after a variable interval showed in almost every case complete healing. In the period intervening between the two operations, inflammatory masses had resolved, fistulæ healed, and enterovesical communications healed spontaneously. The resected specimen showed advanced healing, scar replacement, shrinkage of the lumen, and cessation of evidences of inflammation.

They quoted the following mortality and recurrence rates :—

	Cases	*Mortality (per cent)*	*Recurrence (per cent)*
One-stage resection	55	16·3	19·5
Two-stage resection	25	12·0	36·3
Ileocolostomy with exclusion	65	0	13·8

The diminution not only of mortality, but of recurrence rate also, when treatment is confined to exclusion, in such a large series, and coming, as it were, from the fountain head of knowledge upon this subject, is very impressive. They point out that the apparently greater recurrence rate after two-stage resection is due to the fact that this group includes cases in which simple exclusion had failed to give relief. They advise, therefore, that treatment in the first instance should be by simple exclusion, with resection later only if indicated.

Brown and Donald (1942), on the other hand, found that only 14 out of 45 cases treated by short-circuiting operations remained well.

In this country opinion seems to be in favour of primary resection where possible. Edwards (1948) advocates one-stage resection, except where it is not expedient owing to the patient's poor state of health, or because of fixity of the mass, having experienced a case in which fistula formation occurred after ileocolostomy. Aird (1948) considers one-stage resection for uncomplicated cases, and treats advanced lesions by exclusion.

Experience at the General Infirmary at Leeds bears out this view :—

	Cases	*Deaths*	*Recurrence*
A. Uncomplicated Cases:—			
One-stage resection	20	0	4
Two-stage resection*	2	1	0
Ileotransversostomy	2	0	0
B. Complicated Cases (fistula or intestinal obstruction) :—			
One-stage resection	3	2	0
Two-stage resection	3	1	0
Ileotransversostomy	1	1	0
Ileotransversostomy with exclusion	1	0	0

* General condition poor.

Thus there has been no death after one-stage resection in 20 uncomplicated cases, while 2 out of 3 cases with abscess and fistula formation died after one-stage resection. Two-stage resection was slightly less lethal. Quoted alongside the large series of the American authors these figures do not perhaps bear very great weight : however, they are given for what they are worth, and they do seem to indicate that one-stage resection is a safe procedure in the uncomplicated cases.

Points in Operative Technique.—

1. *Resection of Mesentery.*—In view of the possibility of purely mesenteric recurrence, and of the fact that active inflammation proceeds in the mesentery and glands, it would seem advisable to remove as much of it as possible when a resection is undertaken. Garlock and Crohn (1945), however, speaking from their great experience, say that the recurrence rate is just as high, if not higher, after radical resection with excision of the mesenteric glands.

2. *Exclusion.*—In the absence of obstruction it appears to be safe to close the distal end of the ileum and return it to the abdomen. In the presence of obstruction there is the danger of creating a closed loop, and the distal ileum should probably be left to open on the surface as a ' mucous ileostomy ', to be closed at a later stage after the expected resolution has taken place.

RECURRENCE

Bockus (1945) says that good results are probably not to be anticipated in more than 50 per cent of resections.

In the present series 22 of the 27 patients who survived operation have been traced. Proved recurrence occurred in 4 cases, and a further 3 cases have symptoms suggesting the possibility of recurrence, though radiographic evidence is lacking. Thus 7 cases (32 per cent) were not relieved.

In all these 7 unsatisfactory cases, the primary treatment had been resection. In the 4 cases treated by short-circuit, 2 are well, 1 died as a result of the operation, and 1 is too recent for assessment.

The interval between operation and onset of symptoms of recurrence was 12½ years, 5 years, 4 years, and one month respectively in the four cases.

Pain was the prominent symptom of recurrence in every case. Loss of weight and anæmia are suggestive but not always present. Erratic bowel action may simply be the effect of the previous operation.

The supervention of malignancy in long-standing Crohn's disease has not yet been reported.

AETIOLOGY

This is still quite obscure, and main interest now attaches itself to this question.

1. Tuberculosis.—Most cases of this disease encountered before Crohn's account of 1932 were labelled ' hyperplastic ileal or ileocæcal tuberculosis '. No reference was found, on searching through the records of the Leeds Infirmary, to ' chronic interstitial enteritis ', i.e., ' Dalziel's disease ', or to any other such designation, though the absence of specific tuberculous characteristics was sometimes noted by the histologist in cases in which a diagnosis of tuberculosis was made.

Details of the incidence of hyperplastic intestinal tuberculosis and of Crohn's disease in this hospital during the past 25 years is of interest (*Table IV*).

Table IV.—Showing Incidence of Crohn's Disease and Intestinal Tuberculosis at the General Infirmary at Leeds during 1925–50

	No. of Cases				
	1925–30	1930–35	1935–40	1940–45	1945–50
Intestinal tuberculosis	20	18	19	12	3
Crohn's disease	—	—	3	13	18
	20	18	22	25	21

While the combined incidence has remained more or less constant, tuberculosis has become gradually less common while Crohn's disease has become more frequent. Warren and Somers (1948) express the view that hyperplastic tuberculosis of the intestine is an obsolete term.

There may, however, have been a real increase in the incidence of Crohn's disease. Brown and Donald (1942) believe this to be so. At the Mayo Clinic there were 2 cases in 1922, no more until 1929, and between 1938 and 1942 there were 114. At the same time, improvement in milk hygiene in this country may have reduced the incidence of the hyperplastic form of intestinal T.B., which is generally supposed to be a bovine infection.

It seems fair to say, however, that this condition has in the past been regarded as tuberculous—some still regard it as tuberculous (Taylor, 1945), and in any case the distinction between the two conditions of Crohn's disease and hyperplastic intestinal tuberculosis is very difficult. In many cases the early 'specific' lesions described by Hadfield have been replaced, and the diagnosis then rests upon negative findings—i.e., absence of caseation, absence of tubercle bacilli, and absence of response on guinea-pig inoculation.

2. Reticulosis.—Hadfield (1939) has emphasized the close resemblance between the early lesion in Crohn's disease and Boeck's sarcoidosis, and has tentatively classified it along with the reticuloses (Hadfield and Garrod, 1947).

Williams and Nickerson (1935) injected emulsified sarcoid tissue into the skin of 8 patients: 2 with sarcoidosis gave a positive reaction; 2 others with regional ileitis also gave a positive reaction; while 4 controls were negative.

Calciferol causes regression of sarcoid lesions. In one case in this series, a large abdominal inflammatory mass resolved during the administration of calciferol during a period of three months (*see above*), though it has since recurred.

On the other hand no case of regional ileitis has yet been recorded in which other sarcoid manifestations have been found, e.g., lesions in the skin, lungs, bones of the fingers, generalized lymph-gland enlargement, or splenomegaly, though they were carefully looked for in Blackburn, Hadfield, and Hunt's (1939) series, and in the later members of this series.

Warren and Somers (1948) collected and analysed reports of 50 autopsied cases of sarcoidosis, and found that 7 of them had intestinal lesions. Of these 3 had sarcoid generalized throughout the stomach and bowel, 1 had a localized sarcoid in the descending colon, 2 others had a tuberculous lesion, while 1 had an indeterminate granuloma possibly complicated by syphilis. These writers also report an absence in the giant cells of Crohn's disease of characteristic spiculated bodies seen in the giant cells of sarcoid.

Finally, the predominance of negative Mantoux reactions seen in sarcoidosis has not been found in Crohn's disease.

3. Lymphatic Obstruction.—It has been suggested that disease producing blockage of mesenteric lymphatics may lead to lymphœdema in the bowel wall; secondary infection and ulceration then follow and complete the picture. Either a tuberculous or a non-specific ileocæcal adenitis might act in this way.

The experiments of Reichert and Mathes (1936) lend support to this proposition. They produced intestinal lymphœdema in animals by injecting sclerosing solutions into the mesenteric lymphatics.

Against this is the fact that not all cases of Crohn's disease show proportionate changes in the mesentery. In some the mesentery is not thickened and only a few fleshy glands are seen. On this theory alone, it is also difficult to account for the early specific histological changes.

4. Virus Infection.—It is always natural to suspect that a mysterious virus lurks behind an unknown aetiology. In this condition the lesion appears so obviously inflammatory while bacteria are so conspicuously absent, that the conclusion seems particularly attractive.

Rodaniche, Kirsner, and Palmer (1943) investigated this possibility in connexion with the possible relationship between Crohn's disease and lymphogranuloma inguinale. They reported no evidence to suggest that Crohn's disease was due to lymphogranuloma inguinale or to any other virus. However, they added the proviso that their failure might have been due to the use of unsusceptible animals (they used mice, guinea-pigs, rabbits, and a Rhesus monkey), or to inadequate routes of inoculation (subcutaneous and intracerebral). The Frei test was always negative.

The use of the electron microscope may perhaps prove helpful in this direction.

5. Psychosomatic Factors; Relationship to Ulcerative Colitis.—Many authors have noted the frequency with which the condition occurs in emotionally unstable individuals. Blackburn and others (1939) noted 4 'anxiety states' in 22 cases. Bockus (1945) comments on the prominence of anxiety and emotional immaturity, and observes that these traits are even more pronounced than in ulcerative colitis. Paulley (1948) records 4 cases, all of which showed the abnormal dependance common to duodenal ulcer and ulcerative colitis, and in all of which onset and relapses were related to stress situations.

There may be a relationship between Crohn's disease and ulcerative colitis. Cattel, at the Lahey Clinic, has seen 15 cases in which regional ileitis and ulcerative colitis either followed one another or were coincidental (*Lancet*, leading article, 1948). The operation of emotional factors in ulcerative colitis (Cullinan, 1938) seems now to be accepted.

Lium and Porter (1939) showed that spasm produced ulceration in colonic explants in dogs.

In ulcerative colitis the ileum is affected in about a quarter of cases, but the chronic thickening and stenosis is not seen. Further, lesions of Crohn's disease occurring in the colon do not resemble ulcerative colitis. It would hardly seem that the two conditions can be explained on the same basis alone. The writer of a leading article in *The Lancet* considers that there may be grounds for supposing that regional ileitis, like ulcerative colitis, is a manifestation of an over-active response to an infection, and that its course is determined by emotional and other factors that differ from case to case.

Careful psychiatric investigation is being carried out at present on cases in this series.

6. Other Factors.—Numerous other factors have been suggested as possible aetiological agents. Dalziel drew attention (1913) to the similarity between 'chronic interstitial enteritis' and Johne's disease of cattle—produced by an acid-fast bacillus—while observing that these organisms while abundant in the animal lesions were lacking in the human disease.

Felsen (1936 a, b) isolated the organisms of bacillary dysentery, or obtained positive complement-fixation reactions in a number of cases, and believed this to be the cause; other workers have not confirmed this.

Warren and Somers (1948) remark that the microscopical picture is that of a response to lipid, and suggest that fat-containing chyle may escape from damaged lymphatics and act as a chronic irritant to interstitial tissues.

Cultures of material from the lesions, from the glands, and from the blood have been repeatedly taken and are usually negative, though from time to time organisms are found and arouse suspicion, e.g., *B. coli* (Dalziel, 1913), a streptococcus (Jackman, 1934), a specific organism (Brust and Bargen, 1934).

Patey (1949) has noted in 2 cases that the total length of the small intestine is unusually short—7½ ft. in one case, and 9 ft. in the other. In one of our cases this observation was also made, though the intestine was not measured. It is not easy to ascribe any significance to this observation, unless spasm is capable of producing shortening in the small intestine in the same way as spasm in ulcerative colitis produces shortening in the large intestine.

NOMENCLATURE

Chronic interstitial enteritis (Dalziel, 1913)
Non-specific granuloma (Wilensky, and Moschowitz, 1927)
Regional ileitis (Crohn, 1932)
Regional enteritis
Regional enterocolitis } later variants
Cicatrizing enteritis

All of the above terms, with the exception of Dalziel's original 'chronic interstitial enteritis', are in general use to-day. None of them, except perhaps Dalziel's term, is unexceptionable. It seems contradictory to speak of non-specific granuloma in association with specific giant-cell systems. The adjective 'regional' is more appropriate to geography than pathology, and in any case suggests something widespread; 'segmental' is a better term. The expression 'enterocolitis' is redundant, as 'enteron' embraces the whole intestine. 'Cicatrizing enteritis', though a fair description, is far from euphonious. In any case, most of these terms can be applied equally aptly to diverticulitis.

The name Crohn's disease has been adhered to in most cases at this hospital. It avoids confusion, makes no pretence of pathological exactitude, conveys an exact meaning, is easily remembered by students, and pays a well-deserved tribute.

SUMMARY AND CONCLUSIONS

1. A brief historical survey has been given.

2. A description of the pathology and clinical features has been given, with special reference to a series of 34 cases which have been treated at the General Infirmary at Leeds.

3. In a follow-up of cases of 'acute terminal ileitis', no evidence was found to suggest that it ever becomes chronic or is an early stage of Crohn's disease.

4. Treatment has been discussed. Primary resection is safe in the uncomplicated case; for the difficult case ileocolostomy with exclusion is probably the best treatment.

5. Overall mortality was 18 per cent.

6. Recurrence rate was about 20 per cent.

7. Aetiology has been discussed. The incidence of hypertrophic intestinal tuberculosis and of Crohn's disease has been compared over the past twenty-five years. The conclusion has been drawn that the condition which the pathologist formerly diagnosed as hypertrophic intestinal tuberculosis he now in the majority of cases calls Crohn's disease.

8. The term 'Crohn's disease' is preferred because it is conveniently non-committal.

Our thanks are due to the surgical staff of the General Infirmary at Leeds, who so kindly allowed us to follow up their patients; also to Professor M. J. Stewart for providing the microscopical sections, and to Professor A. S. Johnstone for the X-ray photographs and his helpful comments. We are much indebted to Miss E. M. Wright for the admirable paintings, and to Miss E. Hanson and Miss S. Clark for their secretarial assistance.

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THE FASCIAL SPACES OF THE PALM

WITH SPECIAL REFERENCE TO THEIR SIGNIFICANCE IN INFECTIONS OF THE HAND

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IN this country where so many of our people are manual workers, no surgeon will deny the importance of a sound knowledge of the clinical anatomy of the hand. Many will agree that such knowledge often falls short of the desirable. This is especially true of the fascial spaces of the palm, with which this paper deals. An attempt is made herein to simplify certain topographical conceptions of hand anatomy, the proper understanding of which is essential to successful treatment.

HISTORICAL NOTE

Any reference to the literature must begin with an acknowledgement to Kanavel, Professor of Surgery in Chicago, for his pioneer work in this field. Until the publication of his *Infections of the Hand* in 1912 the presence of the fascial spaces and their relationship to disease had excited little interest. Few relevant facts were recorded by anatomists before this time, despite meticulous attention to detail in this region, for the clinical significance of the cellular tissues far outweighs their anatomical importance. As Dubau (1927) pointed out, the "noble structures" of the hand had held the centre of the stage. Thus it is that in the standard text-books of the late nineteenth and early twentieth centuries little was written about the fascial spaces, and even to-day satisfactory accounts are by no means universal. Thane (1882) had no comment to make. The French anatomists Testut (1889) and Charpy (1901) recorded, in similar words, the presence of three palmar spaces—thenar, middle palmar, and hypothenar. Frohse (1908) agreed that three spaces were demonstrable anatomically, but considered them to be mainly of interest to the surgeon. His views, shared by Testut and Charpy, were that the thenar space contained the intrinsic muscles of the thumb and its long flexor tendon; the hypothenar space contained the intrinsic muscles and long flexor tendons of the little finger, while in the middle palmar space were the remaining flexor tendons and all the lumbrical muscles. The descriptions given were brief and, in the light of recent knowledge, inaccurate.

Kanavel's research extended over twenty years, culminating in the publication of his book in 1912. Using freshly amputated hands from which macroscopical transverse sections were made, he confirmed the existence of these three spaces. By the further study of 56 dissecting-room hands, employing a method of injection of plaster-of-Paris or red lead with subsequent dissection and radiography, their boundaries were carefully determined and their mode of communication with adjacent structures was established. Clinical findings supported his anatomical conclusions.

Thereafter a voluminous literature appeared, concerned mainly with the surgical pathology of this region, and it was not until 1925 when the French surgeon, Iselin, became interested in the surgery of the hand, that any critical review of the anatomical aspect of Kanavel's work was begun. Iselin repeated Kanavel's experiments, using first gelatin and later plaster-of-Paris for injection and dissection, and barium sulphate for injection and radiography. In all, 28 hands were dissected. One serious difference of opinion resulted. Kanavel maintained that the index synovial sheath lay within the thenar space. Iselin placed it in the middle palmar. Dubau attempted to explain the discrepancy, but failed to do so. In Iselin's account there are featured two other palmar spaces, the "anterior middle palmar" and the "commissural". These should not be classed as fascial spaces, although they undoubtedly constitute situations in which pus may become localized: it is not proposed to deal with them herein. Nevertheless, it will be necessary to refer again to the commissural spaces when the lumbrical canals are discussed.

After Iselin's work the results of two further anatomical investigations were published. Best (1929), in America, studied 84 hands, and in a

profusely illustrated but briefly annotated paper supported Kanavel's views. In France, Cordier and Coulouma (1934) followed with a description of their findings in 46 hands and came to conclusions similar to those of Iselin.

A further detailed survey of Kanavel's work was undertaken by the anatomists Grodinsky and Holyoke (1941) in the University of Nebraska. They examined 92 cadaver hands, following Kanavel's methods closely. It is unfortunate that they appear not to have been aware of Iselin's contribution, but their account is excellent and agrees in almost all respects with his. They reviewed the work of Anson and Ashley (1940) and decided that it added little to knowledge of the subject. Finally, Flynn (1942), with 100 cases of fascial space infection and 100 dissections to support his contentions, arrived at a conclusion concerning the septum separating the middle palmar and thenar spaces which differs from that of any preceding. Details of the anatomy of the fascial spaces given by Bunnell (1944) would appear to be based not only on his own findings but on those of workers holding somewhat divergent views. It is not surprising that he should have expressed certain doubts as to the precise mode of separation of these two spaces.

In the account which follows, the findings correspond closely to those of Grodinsky and Holyoke.

METHOD OF STUDY

The description is based on the study of 59 hands in the Anatomical Department of the Medical College of St. Bartholomew's Hospital. Three fresh specimens and 8 fixed cadaver hands were dissected completely. A further 48 hands were examined in the dissecting rooms to confirm points of detail, and of these several were dissected by colleagues to check the findings. For obvious reasons the supply of fresh material was limited. To avoid the pertinent criticism that pressure injection may open up artificial spaces or take a course not necessarily followed by pathological exudates, the method of dissection alone was employed. The value of many otherwise excellent accounts in the literature is offset by the difficulty of following particular structures through a series of macroscopical sections. To illustrate the text it was decided to employ line drawings, made as the work proceeded and representing average findings.

ANATOMICAL FEATURES

1. General Considerations.—Classically there are three main palmar spaces—thenar, middle palmar, and hypothenar. Of these the last will be briefly discussed and rejected. Most authorities are agreed that it is not a fascial space at all. It is an interval separating the intrinsic muscles of the little finger from the palmar aponeurosis, which may be artificially defined by breaking down the fibres that unite them. The same can be said of the term ' thenar space ', for the three muscles of the thenar eminence or *ball* of the thumb bear a similar relationship to the palmar aponeurosis. The anatomical space present on the radial side of the palm is related to the muscles of the *web* of the thumb and will be referred to as the " adductor space " hereafter.

From the forearm to the fingers there is a common pathway for the flexor tendons and their synovial sheaths. Narrow within the carpal tunnel, the pathway broadens suddenly in the palm. At this level on the medial side are the hypothenar muscles. Laterally the two heads of origin of the adductor pollicis pass outwards towards the thumb. In the floor, between these two separate muscle groups, are the 4th, and the adjacent surfaces of the 3rd and 5th, metacarpal bones with the interosseous muscles arising therefrom, the whole being covered by part of the volar interosseous fascia. Forming the roof and extending across the concavity of the palm from ulnar to radial side, and passing beyond the palm on to the ball of the thumb, is the palmar aponeurosis.

Between roof and floor there is a distinct gap, narrow but constantly present and capable of wide separation without the use of the knife. The compartment thus outlined is in turn subdivided by a broad sheet of connective tissue into two smaller compartments—the middle palmar and adductor spaces—and this connective tissue barrier is the oblique septum of the hand. Before describing the spaces and septum in detail it is necessary to consider the palmar aponeurosis.

2. The Palmar Aponeurosis.—The subcutaneous aspect of the palmar aponeurosis is sufficiently well known not to require description. It should be noted, however, that it presents a deeper stratum of fibres distinct from those prolonging the insertion of the palmaris longus tendon. These deep fibres, which are continuous proximally with the distal border of the flexor retinaculum and which end at the level of the superficial transverse palmar ligament, decussate in the centre of the palm. They are absent over the thenar and hypothenar parts of the aponeurosis. On their deep surface they give way to a looser type of connective tissue, blended with that surrounding the flexor tendons and lumbrical muscles, and the superficial vessels and nerves lying between the musculo-tendinous structures and the aponeurotic fibres proper.

The aponeurosis is firmly attached to the bony framework of the hand and it is this portion which escapes notice, although admirably described more than half a century ago by Legueu and Juvara (1892), who advanced the work done by Grapow (1887) and Maslieurat-Lagémard (1839). This attachment is effected by anchoring fibres which arise from those described above. Their direction is dorsal, at right angles to the plane of the palm and parallel to the " pretendinous languettes " of Legueu and Juvara (*Fig.* 273). There are eight separate groups of fibres which sweep dorsally on either side of the flexor tendons of each of the four ulnar digits. In so doing they form a series of aponeurotic septa, one pair to the tendons of each finger. The septa end by fusing with the volar interosseous fascia. To reach this fascia the septa related to the index tendons must pass beyond the distal border of the adductor transversus pollicis, as must the *lateral* septum of the pair to the middle finger and they are correspondingly short. The *medial* septum of the pair for the middle finger, however, is long and obtains attachment to the interosseous fascia upon the entire shaft of the 3rd metacarpal bone. Those

septa related to the tendons of annularis and minimus are also long, for there is no adductor pollicis in their path. That on the medial side of the tendon of the little finger is attached to the 5th metacarpal bone as far proximally as the hook of the hamate and separates the 4th volar interosseous muscle from the opponens digiti minimi. It is also thicker and denser than the others. This is the " internal intermuscular septum " of earlier writers, but, as will be seen, it lies altogether medial to the tendon mass. Superficially its origin corresponds to the junction of the central and hypothenar parts of the palmar aponeurosis. In passing from their superficial to their deep attachments, the individual fibres of the aponeurotic septa are at the same time directed proximo-distally. At the most proximal level at which these fibres appear, each of the seven lateral septa presents a sharp, crescentic border and in this respect also they differ from the internal intermuscular septum.

As each pair of septa extend distally they end upon the sides of the fibrous digital sheaths at the level of the neck of the metacarpal bone, and upon the deep transverse metacarpal ligaments. The tendons of the middle, ring, and little fingers are thus held firmly in place as they traverse the palm until the appropriate fibrous digital sheath is entered and even in extreme lateral movements at the wrist-joint cannot shift from their positions. They run, as it were, within a continuous aponeurotic sleeve and angulation is prevented. The same cannot be said of the index tendons, for their aponeurotic septa are short; but, as will be shown, they are provided with a restraining mechanism peculiar to themselves in the shape of the oblique septum.

It is interesting to consider that the relative frequency of involvement of the digits in Dupuytren's contracture, as given by Bunnell (and J. S. Davis, whom he quotes), is almost directly proportional to the quantity of connective tissue in the aponeurotic septa and pretendinous fibres of the digit concerned.

3. The Oblique Septum.—The oblique septum is a thin and occasionally almost transparent sheet of connective tissue, roughly quadrilateral in shape, distinct from the aponeurotic septa described above. Its superficial and deep attachments are precise, while proximally and distally it shades off gradually into neighbouring structures. It arises from the volar surface of the 3rd metacarpal bone in common with the origin of the adductor transversus pollicis and the insertion of the more medial of the two aponeurotic septa of the medius tendons. Distally the oblique septum blends with the capsule of the 3rd metacarpophalangeal joint, the deep transverse metacarpal ligament uniting the 2nd and 3rd metacarpal bones and the fibrous sheath of the index finger. Proximally it fuses with the volar interosseous fascia and in the carpal tunnel is lost in the connective tissue between the origin of the adductor obliquus and the deepest layer of the flexor mass.

From its origin the oblique septum passes in the same direction as the fibres of the adductor transversus pollicis but at an acute angle to them, so that septum and muscle gradually diverge. Between them there appears a V-shaped interval—the most medial part of the adductor space. In this interval there are flattened lobules of soft, yellow fat, lying cushion-like between the septum and the adductor epimysium. The septum ends by joining the under surface of the palmar aponeurosis along a line corresponding to the radial longitudinal crease of the palmar skin. In so doing, it splits to enclose the index tendons and 1st lumbrical muscle, a certain quantity of synovial-like fat, and portions of the digital and palmar serous sheaths of these tendons. So thin is the septum as it passes around the lateral side of these structures that the outline of the muscle can be readily seen, while close to the line

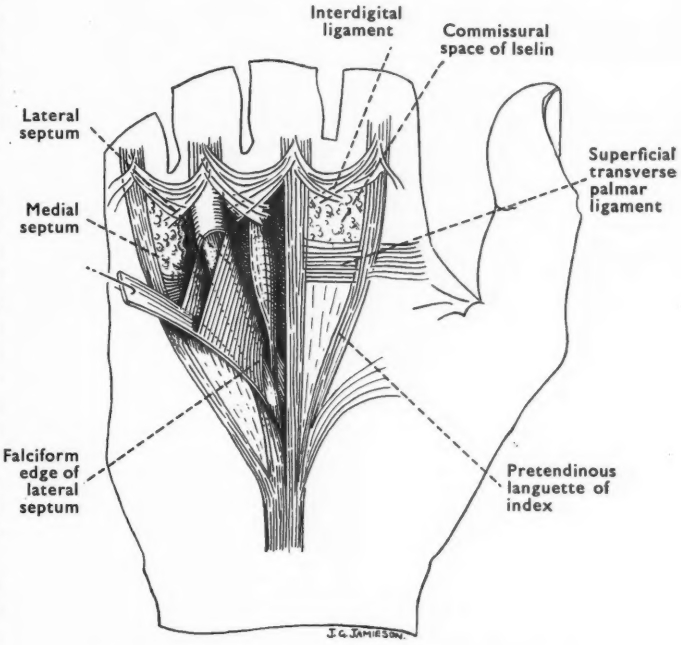

FIG. 273.—The superficial aspect of the central part of the palmar aponeurosis in diagrammatic form. The pretendinous languette of the ring finger has been separated from the fibrous digital sheath and drawn upwards and medially to show the lateral and medial aponeurotic septa. The interdigital and superficial transverse palmar ligaments are also seen.

of fusion with the palmar aponeurosis there can be discerned the branch of the median nerve destined for the lateral side of the index finger (*Fig.* 274). On the medial side of the index tendons there lie the other tendons within their synovial and connective-tissue coverings. Here the septum passes medially to become indistinguishable from the fine, membranous layer of connective tissue forming the immediate roof of the middle palmar space. The index tendons and their coverings are thus situated in the lateral extremity of the septum, from their emergence from the carpal tunnel to their entry into the fibrous sheath of the finger. The 1st lumbrical muscle is similarly enclosed until it leaves the tendons near the distal border of the adductor transversus pollicis, at which level the first of the aponeurotic septa descends to render the divergence complete.

4. The Fascial Spaces.—From the foregoing the exact boundaries of the fascial spaces can be determined. It is necessary at the outset, however, to note that they are situated with their adjacent

borders overlapping in the midline of the palm, the adductor space deep to the middle palmar, so that an instrument passed through the palm between

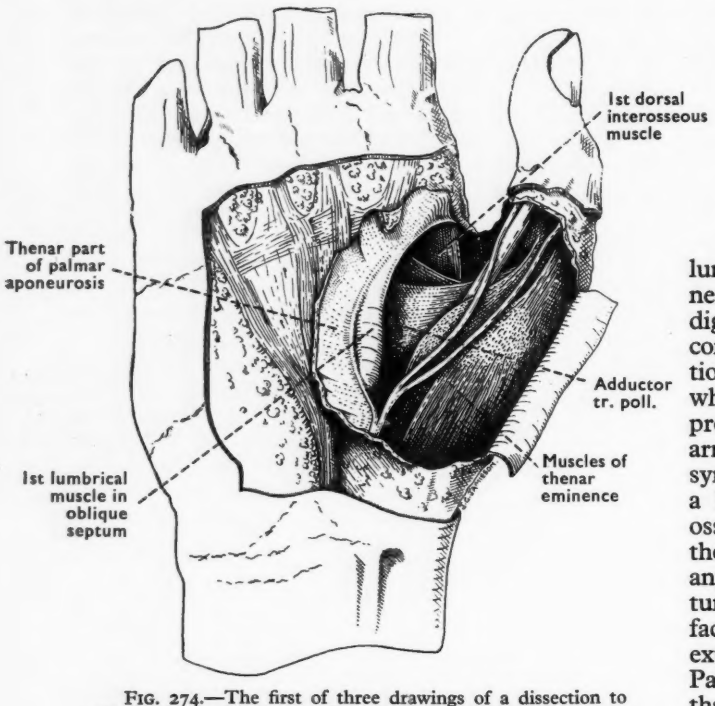
1st dorsal interosseous muscle
Thenar part of palmar aponeurosis
Adductor tr. poll.
Muscles of thenar eminence
1st lumbrical muscle in oblique septum

FIG. 274.—The first of three drawings of a dissection to display the fascial spaces. The thenar part of the palmar aponeurosis has been cut and reflected to show the intrinsic muscles of the thumb. On the deep surface of the aponeurosis the 1st lumbical muscle is seen shining through the lateral extremity of the oblique septum.

index and medius tendons would enter each space in turn, and between them would pierce the oblique septum (*Fig.* 275).

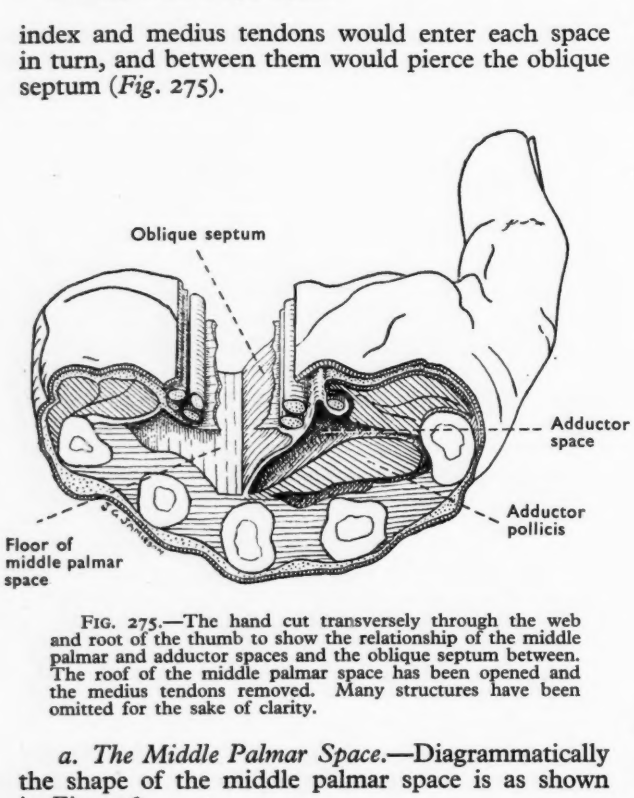

FIG. 275.—The hand cut transversely through the web and root of the thumb to show the relationship of the middle palmar and adductor spaces and the oblique septum between. The roof of the middle palmar space has been opened and the medius tendons removed. Many structures have been omitted for the sake of clarity.

a. The Middle Palmar Space.—Diagrammatically the shape of the middle palmar space is as shown in *Fig.* 276.

The medial wall comprises the eighth or most medial of the aponeurotic septa. *The lateral wall* formed by the oblique septum makes an obtuse angle with the plane of the floor. *The floor* is formed by the volar interosseous fascia covering the interosseous muscles of the 3rd and 4th intermetacarpal spaces and the 4th metacarpal bone. It is much narrower than the roof. *The roof*: the central part of the palmar aponeurosis forms the roof and extends from the lateral border of the hypothenar eminence to the radial longitudinal crease of the palm. In it are the superficial and deep flexor tendons of the 3rd to 5th digits, the 2nd, 3rd, and 4th lumbrical muscles, and the superficial vessels and nerves destined for the 2nd, 3rd, and 4th interdigital clefts. *Proximally* roof and floor are in contact, so that there is virtually no communication between the middle palmar space and that space which is commonly described as overlying the pronator quadratus muscle in the forearm (deep forearm space of Parona). Between the tendons in their synovial sheaths and the ligaments of the carpus is a layer of fascia continuous with the volar interosseous fascia. Fat fills the interstices between these fascial and ligamentous structures, obliterating any possible gaps between the floor of the carpal tunnel and its contents. It is an established surgical fact that infection of the middle palmar space can extend directly into the deep forearm space of Parona. It would appear from these considerations that such an extension can only take place *pari passu* with the liquefaction of the packing tissues in the floor of the carpal tunnel, or via deep lymphatic channels. Proximal spread along the serous sheaths is said to be more common and from the anatomical point of view is the more likely occurrence. *Distally* the aponeurotic septa divide the middle palmar space into several smaller spaces. As the longest of the

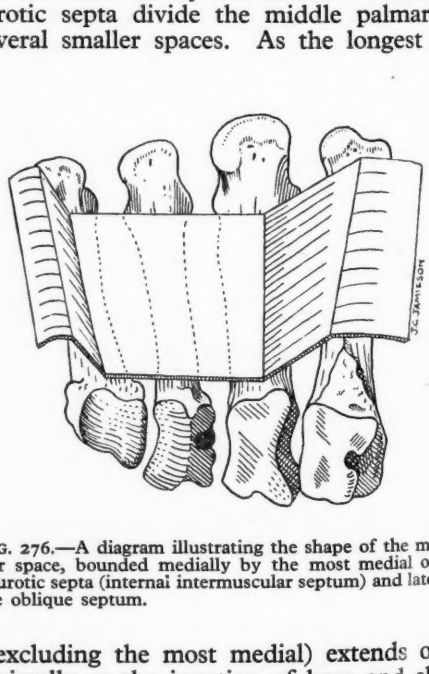

FIG. 276.—A diagram illustrating the shape of the middle palmar space, bounded medially by the most medial of the aponeurotic septa (internal intermuscular septum) and laterally by the oblique septum.

septa (excluding the most medial) extends only as far proximally as the junction of base and shaft of the metacarpal bone, the space is continued uninterruptedly from medial to lateral wall proximal to this level. Here the deep volar arch and deep division

of the ulnar nerve pass transversely, embedded in the interosseous fascia.

The flexor tendons reach the floor of the space at the neck of the metacarpal bone where each pair enters a fibrous digital sheath, so that in these situations the space ceases to exist. Between the tendons there pass the 2nd, 3rd, and 4th lumbrical muscles, which at this same level come to occupy what little interval remains between roof and floor. Beyond the deep transverse metacarpal ligament, lumbrical and interosseous muscles meet, and fibres of the dorsal aponeurosis, sweeping ventrally in the interdigital clefts, join the interdigital ligaments in the webs of the fingers. Each lumbrical muscle is bounded laterally and medially by one of the aponeurotic septa, and these prolongations of the middle palmar space constitute the lumbrical canals.

The labile fat enclosing each lumbrical muscle at its origin is continued upon it, always separated from the epimysium by a narrow interval crossed by fine connective tissue trabeculæ—a primitive form of synovial sheath. The fat, much diminished in amount, accompanies the muscle into the digit to blend with the subcutaneous fat. On the dorsal surface of the muscle, where it traverses the roof of the middle palmar space and more distally where it has reached the floor, this perimuscular fat is reduced to a thin layer. The quantity of fat is increased as it gains the volar surface of the muscle and there surrounds the digital vessels and nerves, becoming superficial between adjacent pretendinous languettes and the interdigital and transverse palmar ligaments. The three fatty quadrilaterals thus outlined are the " commissural spaces " of Iselin (*Fig.* 273). There is no anatomical ' dead space ' at the exit of the lumbrical muscle from the palm, as the term ' canal ' infers, unless the capillary interval between it and its ensheathing fat can be so called. There exists only a potential pathway through cellular connective tissue which may offer little resistance to invading micro-organisms. The subcutaneous fat of the 3rd, 4th, and 5th fingers and that of the commissural spaces may thus become portals of entry to the middle palmar space. It should be observed that the proximal culs-de-sac of the digital synovial sheaths of medius and annularis (and of minimus in at least one-third of cases) extend into the middle palmar space immediately proximal to the heads of the metacarpal bones.

b. The Adductor Space.—Like the middle palmar space, the adductor space has two sides, a roof, and floor. It is roughly wedge-shaped, the apex of the wedge lying along the shaft of the 3rd metacarpal bone, the base at the 1st metacarpal bone and medial border of the muscles of the thenar eminence, so that the space is practically confined to an area overlying the adductor pollicis muscle. *The medial wall* is formed by the oblique septum, the fusion of the distal border of which in the manner described above, limits the space medially and distally. *The lateral wall* is less accurately defined. It comprises the three muscles of the thenar eminence, at the line of contact of the adductor obliquus and opponens pollicis. Proximally, however, the opponens and short flexor muscles of the thumb extend medially towards their carpal and retinacular attachments, so that they come to lie also in the roof. *The floor*, formed by the epimysium on the volar surface of

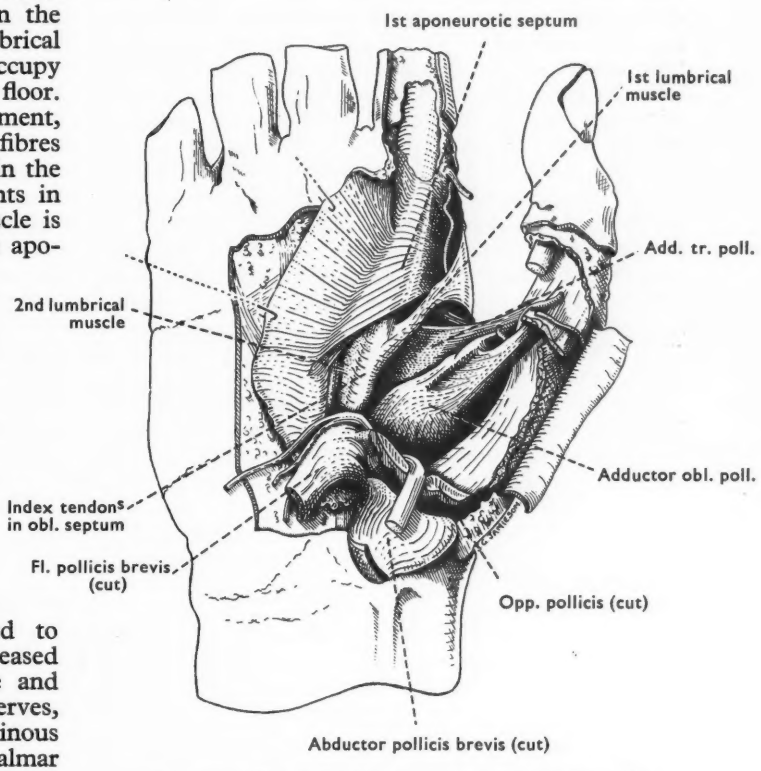

FIG. 277.—The dissection featured in *Fig.* 274 is carried a stage farther. The muscles of the thenar eminence have been cut and turned back. The floor of the adductor space is displayed except for its medial extremity, which remains hidden by the index tendons in the oblique septum. The first of the aponeurotic septa is pulled over medially by the further reflection of the palmar aponeurosis.

the adductor pollicis, is considerably broader than the roof. *The roof* is narrow and triangular in outline, with apex directed proximally. It comprises that portion of the palmar aponeurosis which extends between the radial longitudinal crease medially and the web of the thumb and summit of the thenar eminence laterally. As the aponeurosis passes towards the dorsum of the 1st metacarpal bone it becomes more and more closely adherent to the underlying epimysium of the pollical short flexor and short abductor. Along the line of fusion of roof and medial wall are the flexor tendons of the index finger and the 1st lumbrical muscle (*Fig.* 277). *Proximally* the space is gradually obliterated (as in the case of the middle palmar space) by the meeting of roof and floor. At this level, corresponding to the distal border of the flexor retinaculum, there escape from the carpal tunnel those branches of the median nerve supplying the muscles of the ball of the thumb; its two cutaneous branches and the nerve to the lateral side of the index finger. The cutaneous nerves are embedded in the roof of the space, while the tendon of flexor longus pollicis, contained within the radial bursa, passes across the floor.

Distally and laterally the adductor space terminates by the fusion of the dorsal and palmar aponeuroses along the outer border of the 1st dorsal interosseous muscle, these structures being particularly firmly blended with each other and with the dorsal interosseous fascia at and beyond the head of the 2nd metacarpal bone. Between the adductor transversus and 1st dorsal interosseous muscles, however, there is finer connective tissue, the trabeculæ of which may be readily broken down to produce a wholly artificial extension of the adductor space between these muscles, and for a short distance on to the dorsum of the hand over the web of the thumb. The 1st lumbrical muscle enters the index finger beyond the distal border of adductor transversus, and in leaving the space is closely interposed between the roof and floor.

THE INDEX TENDONS AND 1st LUMBRICAL MUSCLE

It has been shown, and it is emphasized, that these structures are neither wholly in one space nor in the other (*Fig.* 278). Much time has been spent by various past investigators in attempts to correlate evidence proving that proximal spread of infection along the index synovial sheath or the 1st lumbrical canal involves the adductor space in some cases and the middle palmar space in others. The answer is to be found in the anatomy of the part. The index tendons pass through the lateral border of the oblique septum and so occupy a *common wall* between the two spaces. It would seem that infection reaching the proximal cul-de-sac of the index synovial sheath would naturally tend to spread through the thinner lateral wall of the oblique septum and involve the *adductor* space, but there would appear to be no reason why the thicker cellular tissues on the medial side of these tendons should not undergo softening, the infection then entering the *middle palmar* space.

In so far as the first lumbrical muscle is concerned, infection of the subcutaneous fat of the index finger would have little difficulty in extending into the *adductor* space. Should spread of the infection continue proximally along the lumbrical sheath then the lateral extremity of the oblique septum would be entered. The fibres of origin of this lumbrical arise not only from the lateral side of the tendon of flexor profundus digitorum but from its superficial and deep surfaces. Not uncommonly these fibres also obtain origin from the sublimis tendon. It would appear possible for an infection confined initially to the lumbrical sheath to extend finally into the fat enclosing the index tendons and so through the medial side of the oblique septum into the *middle palmar* space. Despite these alternatives, there is obviously a greater risk of involvement of the *adductor* space from the index synovial sheath and 1st lumbrical canal. It has been stated that the oblique septum is occasionally thin. In such cases it is easy to envisage its eventual rupture with spread of infection throughout the depths of the palm.

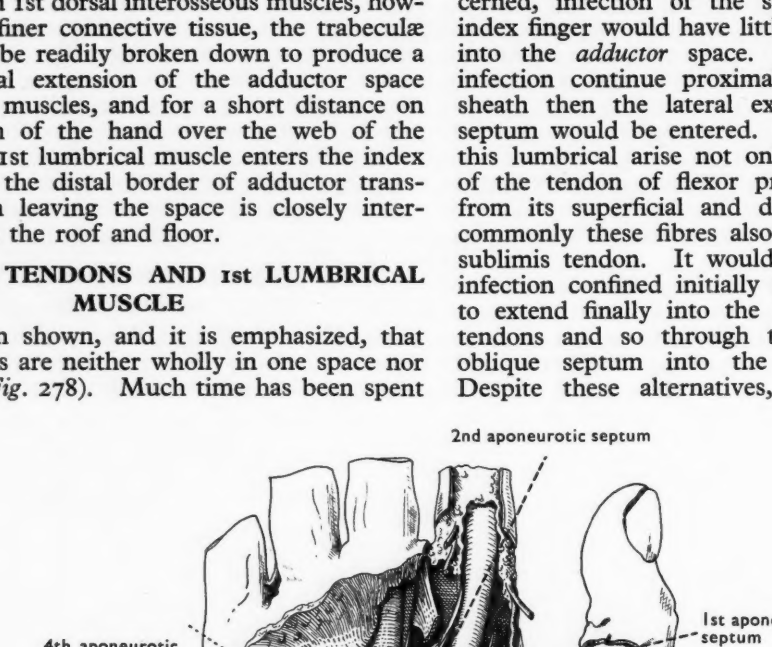

FIG. 278.—The final stage of the dissection shown in *Fig.* 277. The first three aponeurotic septa have been cut and the palmar aponeurosis, thus freed, has been drawn farther medially. The 2nd lumbrical muscle and the tendons of the middle finger have been cut and displaced to show the oblique septum with the index tendons in its lateral border. The aponeurotic septum on the medial side of the tendons of the middle finger is seen. The rest of the middle palmar space which lies beyond this septum remains hidden, but can be entered proximal to its free edge.

CONCLUSIONS

From the present investigation it is certain that the oblique septum is not synonymous with the fascia ensheathing the intrinsic muscles of the

thumb, as some writers have suggested. Neither is it one of the anchoring septa described above. The older term 'external intermuscular septum' is misleading for its implied similarity to that which forms the medial wall of the middle palmar space, which continues to be called the 'internal intermuscular septum'.

In his monograph on the hand, Wood Jones (1919) points out that fascial condensations are always present between structures moving in different planes or at an angle to each other. If the presence of an oblique septum in the hand is due to this fact alone then it will be agreed that there is no equivalent in the foot, although the muscles of the hallux and the flexor tendons cross in different planes and at various angles. The hallux, however, has not the mobility of the thumb. The freely-moving adductor pollicis may then have occasioned the formation of this septum, interposed between that muscle and the flexor mass as a whole. If so, it must be acknowledged that despite the mobility of the adductor pollicis, unspecialized connective tissue is found between its deep surface and those muscles of the 1st and 2nd intermetacarpal spaces. Some other explanation must be sought.

It is possible that the oblique septum is a direct outcome of the tendency to specialization of the index finger in man, to which Wood Jones calls attention—a phenomenon which he describes as a "progressive" variation. He emphasizes the separation from their neighbours of the muscle masses moving both flexor and extensor tendons of this digit, and, from a consideration of the flexure lines alone, maintains that the index is unique. Charpy was definite as to the existence of a "posterior median palmar bursa" (distinct from the radial and ulnar bursæ of the palm) present in 80 per cent of the hands he examined, deep to and serving only the index tendons, and he recorded the not infrequent appearance of a similar serous sheath, the "anterior median palmar bursa", between the superficial and deep tendons of this finger.

It is now considered that the oblique septum may well be a retention band for the index tendons, a hypothesis which accords with the evidence already advanced for the tendency to specialization of this finger. Had the index never acquired its distinctive relative mobility then such a structure would not have been evoked and the indical tendons would have remained, like their fellows, anchored by extensive aponeurotic septa. As has been shown, however, the septa which the indical tendons do possess are extremely short; are situate beyond the adductor transversus pollicis, and so can have but little effect upon the tendons in their passage through the palm. The accepted subdivision of the main palmar compartment into middle palmar and adductor spaces would appear to be wholly fortuitous.

SUMMARY

1. A brief review is presented of events leading to the recognition of the fascial spaces of the palm.

2. Without recourse to the pressure-injection technique characterizing earlier work, it has been possible clearly to demonstrate the anatomy of the middle palmar and adductor spaces and that of the oblique septum effecting their separation. A detailed account is given of the means whereby each of these spaces may communicate with adjacent structures.

3. No acceptable explanation for the presence of the oblique septum has been found in the literature, although its existence has long been recognized. Arguments are now advanced for regarding it as a retention band for the index tendons having a definite functional role, and the subdivision of the palm is considered to be secondary.

4. A fresh conception of the lumbrical canals is offered and reasons are suggested for the present difference of opinion concerning the relationship of the 1st lumbrical muscle and index tendons to the adductor and the middle palmar spaces.

5. Attention is drawn to a rather neglected aspect of the palmar aponeurosis—namely, its deep aponeurotic septa, with which the surgery of Dupuytren's contracture is intimately concerned.

6. Conclusions are based upon a strictly anatomical foundation, certain inferences regarding the spread of palmar infections being made therefrom.

Acknowledgements are gratefully tendered to Professor Sir James Paterson Ross, K.C.V.O., for much kindly and helpful criticism; to Professor A. J. E. Cave, for Departmental research facilities; to Mr. F. R. Wilde, for various suggestions; and to Mr. J. L. Thornton, Librarian of St. Bartholomew's Hospital Medical College.

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RESECTION AND RECONSTRUCTION OF THE INTRATHORACIC TRACHEA

By RONALD BELSEY, Bristol

The intrathoracic portion of the trachea is the last unpaired organ in the body to fall to the surgeon, and the successful solution of the problem of its reconstruction may mark the end of the 'expansionist' epoch in the development of surgery.

There are on record several cases from which cylindromatous tumours of the upper third of the trachea have been resected, usually after a permanent tracheotomy has been performed, but in Crafoord's (1945) case the cervical trachea was reconstructed with a skin-flap containing an implant of costal cartilage. Diligent search has brought to light no account of a successful radical resection of the intrathoracic trachea in the human being, other than the case briefly reported by the author in 1946. This case will now be reported in greater detail, together with an account of a second case. To have reported these cases earlier, before an adequate follow-up survey had been conducted, would have contributed little to the surgery of the trachea. Too often in the past the premature publication of newly devised operations has led to disappointment and ill-merited discredit.

The delay in the attack on this organ can probably be attributed to three main factors: First, as in the case of the heart, its function cannot be suspended even temporarily, and an adequate airway must be maintained throughout. Second, the healing properties of the trachea have been suspect, as in the case of the major bronchi, on account of the large amount of cartilage in its structure. Third, no satisfactory method of by-passing this organ, as exists in the case of the cervical trachea, has been evolved up to the present time.

The advance of modern anæsthesia and the introduction of bronchial intubation has gone far towards the solution of the first problem. Any doubt concerning the healing properties of the trachea has been dispelled by the satisfactory results obtained when part of the trachea adjacent to the carina is resected during a total right pneumonectomy. Simple approximation of the edges of the defect with non-irritant suture material leads to healing without reinforcement of the suture line with pleura, fascia, or adjacent mediastinal tissues. The same is true of the major bronchi, as demonstrated by Griffith (1949).

The difficulty of by-passing the intrathoracic trachea remains unsolved, and any extensive resection must be followed by a plastic reconstruction with restoration of continuity.

Little experimental work on the problem has been reported, but in 1940 Taffel published the results of some experiments that are relevant. Following resection of portions of the tracheal wall 1 cm. square in dogs, and closure of the defects with patches of fascia, he demonstrated complete regeneration of the ciliated columnar tracheal mucosa over the inner surface of the patch within two weeks of operation. The fascia fragmented and was absorbed, mucous glands appeared in three weeks, and small islands of new cartilage in four weeks, but there was no attempt at regeneration of the cartilaginous scaffolding of the trachea. None of his animals succumbed to the operation, and no stenosis of the trachea resulted.

The experimental demonstration of a fact long suspected by thoracic surgeons—the rapidity with which ciliated tracheal and bronchial mucosa can regenerate and spread over raw surfaces—is of paramount importance in the evolution of the technique of tracheoplasty. Healing of the repaired defect was complete at four weeks, and in animals sacrificed after this period, three distinct layers could be demonstrated in the area of the graft: (1) An inner layer of pseudostratified ciliated columnar epithelium; (2) A layer of submucosa with occasional mucous glands, a few small islands of cartilage, but no muscle tissue; (3) An outer layer of supporting adult connective tissue.

The only essential structure lacking was a rigid cartilaginous skeleton.

Daniel (1948) has repeated the work of Taffel and confirmed his results. In another series of experiments performed by Daniel on dogs, segments of the trachea were resected and the gaps bridged by tubes of glass or metal. Fifteen animals survived the operation, and the tubes were well tolerated up to six months, when the animals were sacrificed. Daniel was able to demonstrate some attempt at regeneration of the cartilaginous rings in the fibrous tissue surrounding the tubes, but the regenerated mucosa, when present against the outer surface of the tubes, was of a flattened or stratified type, and no cilia were seen. The regenerating mucosa showed no tendency to line the tubes. In one animal from whom the right lung and bronchus were resected, as well as the lower third of the trachea, the tube was removed through a bronchoscope eight months after operation, and when the animal was sacrificed at fourteen months the regenerated mucosa was composed of one or two layers of flat epithelial cells, but no ciliated columnar cells or goblet cells could be demonstrated. The presence of the tube within the lumen of the reconstructed trachea seems to have inhibited the regeneration of the normal tracheal mucosa.

Clagett (1946) resected three to eight segments of the trachea in 22 dogs, and bridged the gaps with polythene tubes over which approximation of the cut ends was attempted under tension. Loosening of the tube resulting in obstruction, or obstruction by granulation tissue, led to the death of some of the dogs, but in 2 dogs killed six weeks after operation there was evidence of only slight inflammation. Following removal of the tube from the lumen through the bronchoscope, 1 dog died immediately from collapse of the trachea, and in

2 others the tube had to be replaced. Only 1 dog tolerated removal of the tube. Clagett could demonstrate no evidence of cartilage in the tissues bridging the gap, nor any regeneration of the ciliated mucosa.

A patient of 49 on whom Clagett (1948) performed a right pneumonectomy and resection of part of the trachea for a cylindroma in the lower third, and on whom this method of reconstruction was carried out, died on the sixth post-operative day from bronchopneumonia.

The acceptability of certain metals, notably stainless steel and tantalum, to living tissues, has been ably demonstrated by Wu and Pai (1942, 1943), and by numerous other experimental workers. The absence of inflammatory reaction permits regenerating living tissues to flow around and engulf small masses of these metals in a way that suggested the possibility of providing Taffel's grafts with the one structure they lacked—a rigid skeleton to maintain the patency of the trachea against pressure from adjacent organs, or during phases of raised intrathoracic pressure.

The essential characteristics of a reconstructed airway are: (i) Lateral rigidity; (ii) Longitudinal elasticity and flexibility; (iii) An adequate and airtight lumen; (iv) An uninterrupted lining of ciliated columnar epithelium.

The importance of the tracheal mucosa has been underestimated. The trachea is a drain as well as an air-duct, and the drainage system depends in large measure upon the function of the ciliated columnar mucosa. Interruption of the ciliary 'escalator', its destruction or replacement by squamous epithelium, may lead to chronic pulmonary suppuration and bronchiectasis, as occurred so frequently when metaplasia followed healing of gummatous ulcers of the lower trachea. Whatever method of reconstruction is adopted, an uninterrupted ciliated mucosal lining is probably essential to success, and for this reason any method based on the principle of an indwelling tube which cannot be incorporated in the regenerating tissues, and so permit complete regeneration of the normal mucosa, will probably lead to progressive pulmonary sepsis.

It is unlikely that sleeve resection followed by end-to-end anastomosis will be feasible in the treatment of any condition calling for a radical resection of the trachea, owing to the tension on the suture line if more than three or four segments are resected, but it may become the procedure of choice in the treatment of inflammatory or traumatic strictures.

A method of reconstruction has been devised in which a free fascial graft supported on a skeleton of a coil of stainless steel wire forms a flexible non-collapsible airtight tube, on the inner surface of which regeneration of normal tracheal mucosa can proceed without interruption, while an adequate airway is maintained. The method has been used in two cases, which will be described, with satisfactory functional and anatomical results. In each instance, as the lumen of the tube became epithelialized, so the wire skeleton became incorporated in the tissues, covered by the epithelium, to maintain lateral rigidity and patency. Other forms of metal prosthesis were considered, but none appeared to fulfil more completely the criteria laid down than the simple coil form.

The indications for radical resection are uncommon. Only primary tumours of the trachea are of practical importance, though it is recognized that other lesions—congenital, traumatic, or inflammatory—may call for resection at times.

Fortunately, primary tumours of the trachea are rare. Schmidt could find only 3 amongst 2088 tumours of the upper air-passages. Ellman and Whittaker (1947) recently reviewed records of 507 cases reported up to 1945. Negus, in a personal communication to Ellman, stated that he had encountered only 5 cases. Twenty-seven cases have been reported from the Mayo Clinic, and isolated cases have been described by a number of authors. By contrast, tumours of the bronchi are diagnosed so frequently that they are no longer considered worth recording.

Unfortunately, however, tracheal tumours are diagnosed only late in the disease, owing to the fact that until 75 per cent or more of the lumen is obstructed, the dyspnœa, cough, and wheeze do not usually become sufficiently severe to distress the patient. Most of the recorded cases have been diagnosed at autopsy, or shortly before death; in every instance the disease was far advanced when the diagnosis was confirmed, and only palliative irradiation or endoscopic electrocoagulation was possible. Few of these tumours show any response to X-ray therapy. Hæmoptysis, which is uncommon during the early stages, might lead to the discovery of an operable tumour. Most are malignant, and even were the significance of Jackson's aphorism that "all is not asthma that wheezes" more widely recognized, and the technique of radical resection perfected, it is anticipated that the late results of operation would be disappointing, although the symptomatic relief that follows restoration of an adequate airway may fully justify palliative resection.

The recorded observations on the nature of primary tracheal tumours emphasize the confusion that exists in their classification. Culp (1938) decided that only 95 out of 433 cases he reviewed were malignant. Of the 27 cases reported from the Mayo Clinic, 19 were highly malignant, and 8 fell into the group known as cylindromata, tumours locally malignant with a tendency to lymphatic metastasis late in the disease. Whether a benign adenoma occurs in the trachea seems doubtful, but the majority of so-called adenomata belong to the group known as cylindromata, and radical resection is necessary for their cure.

The histology of these tumours need not be discussed here, and only the gross pathological features relevant to the practical problem of tracheal resection need be considered. In 70 per cent of cases the tumour is situated in the middle or lower third of the trachea, usually on the posterior wall. Annular growths are rare, and the cartilaginous rings form no barrier to the vertical spread of these tumours in the line of the trachea. Lymphatic spread is backwards towards collecting channels ascending the posterolateral wall in close relationship to the recurrent laryngeal nerves.

Two cases in which an attempt was made to observe the four criteria mentioned earlier in reconstructing the intrathoracic trachea following extensive resections for cylindromatous tumours, will now be described.

CASE REPORTS

Case 1.—In 1944 a female patient of 42 was admitted to a thoracic unit complaining of wheeze and non-productive cough. Two years previously a " cyst " was said to have been removed from the trachea through the bronchoscope and the patient received a course of X-ray therapy lasting three months.

On Examination.—The patient was emaciated; stridor was marked, but there were no abnormal signs in the chest, no evidence of metastasis, and a radiograph of the chest showed no gross abnormality (*Fig.* 279).

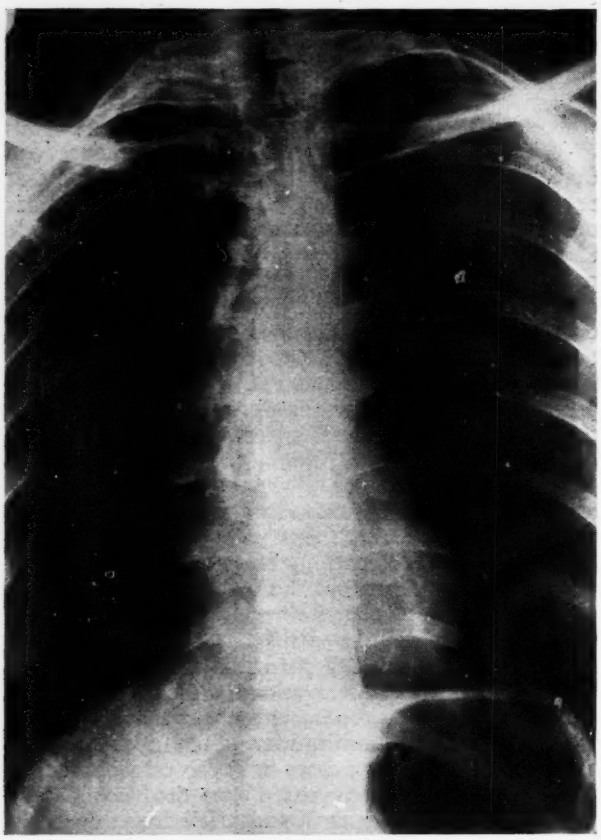

Fig. 279.—Radiograph of chest showing no gross abnormality.

Bronchoscopy revealed a tumour having the typical appearance of a bronchial adenoma, almost completely obstructing the lower third of the trachea and growing from the right wall. A biopsy specimen was reported to show a " benign tracheal adenoma ". Bronchoscopy and biopsy were repeated and the same report returned.

At Operation.—On Sept. 25 a right transpleural thoracotomy was performed, and a portion of tracheal wall measuring 1 × ¾ in, bearing the tumour and its base, was excised. It was thought that some tumour remained on the anterior wall of the trachea, but any further resection threatened to destroy the rigidity and patency of the organ. The defect was closed by a free graft of fascia from the thigh, according to the technique of Taffel (1940).

Progress.—Convalescence was uneventful and the patient's symptoms were completely relieved.

A year later, in 1945, the patient was re-admitted with a recurrence of the tumour at the same site, and a return of the wheeze and cough. A biopsy specimen showed the same histological appearance of a benign adenoma. The stridor became rapidly worse and an extensive resection of the trachea and reconstruction were planned.

Second Operation.—The trachea was again approached through the right pleura. The tumour appeared to have extended up and down the right, anterior, and posterior walls of the trachea, which were extensively infiltrated, but the left wall did not appear to be involved. The greater portion of the trachea, but for a narrow strip ¼ in. wide from the left-hand wall, was excised from a point ½ in. below the thoracic inlet down to the carina. All the tumour-bearing tissue appeared to have been removed.

The trachea was then reconstructed by the method illustrated in *Fig.* 280.

The intratracheal tube was advanced and its tip inserted into the left main bronchus. Unfortunately the

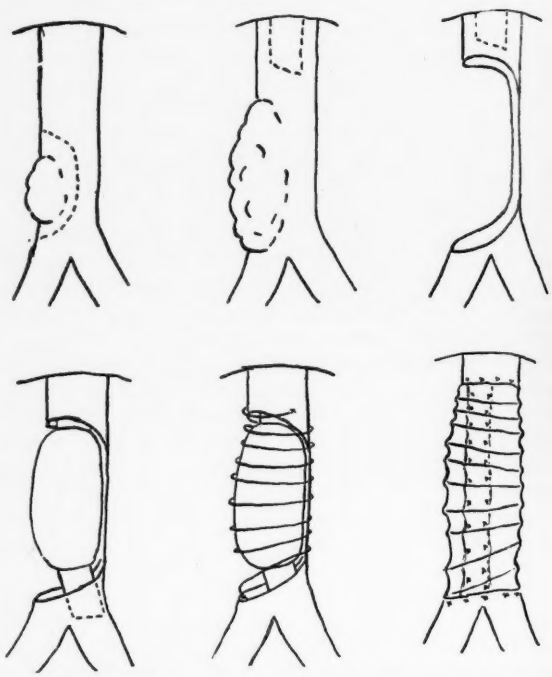

Fig. 280.—*Case* 1. First diagram shows extent of resection at first operation. Remainder show extent of the recurrence one year later, the extent of the resection, and the method of reconstruction with wire and fascia.

cuff was not long enough to occlude the defect during the reconstruction. A coil of 32 gauge stainless steel wire was constructed over the cuff of the intratracheal tube, passing outside the remaining strip of tracheal wall, and anchored with interrupted sutures of the same material to this strip and the cut ends of the trachea. A free graft of fascia from the right thigh was wound firmly around the wire ' skeleton ', sutured with an overlap down the length of the defect and also to the cut edges of the trachea above and below the defect. The trachea was then allowed to fall back into the mediastinum, the right lung was inflated, and a drainage tube inserted through a stab wound in the ninth interspace. Following removal of the intratracheal tube the airway seemed to be normal and the patient's condition was good. Next day air was leaking through the underwater seal, and it was obvious that the trachea had sprung a leak. The right chest was reopened under general anæsthesia and a small leak at the top of the reconstructed trachea was closed with further wire sutures, and the upper lobe of the right lung was sutured to the mediastinum to reinforce the repair. The fascial graft appeared viable.

Progress.—Convalescence was remarkably smooth and uneventful, but for a dry cough for the first two weeks. At no time was there any evidence of infection in the reconstructed trachea.

FIG. 281.—*Case* 1. Lateral view of chest one month after resection and reconstruction, showing the wire 'skeleton' of the intrathoracic trachea.

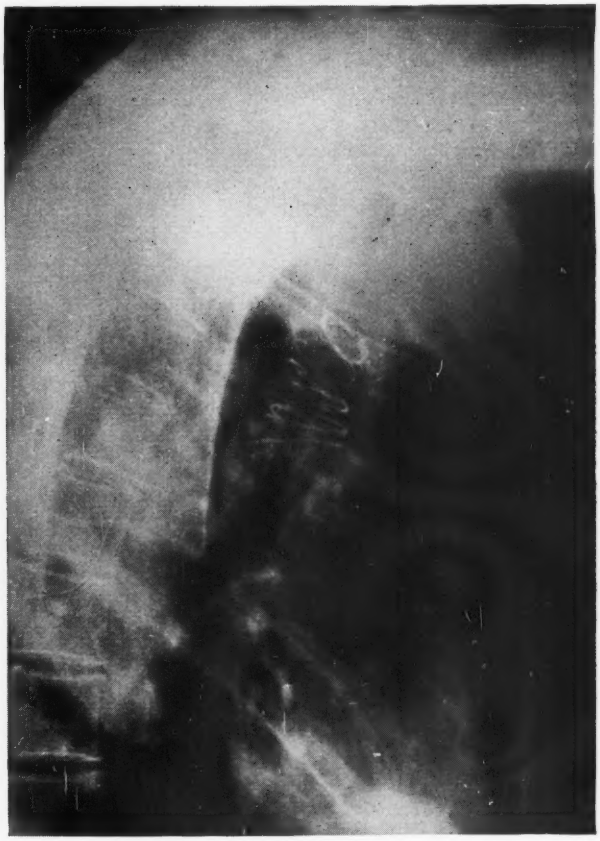

FIG. 282.—*Case* 1. Radiograph one year later, at time of second admission, showing some longitudinal contraction of the reconstructed trachea.

Three months after the operation the patient was leading a normal life and was free from symptoms. A bronchoscopy performed at that time showed that the reconstructed segment was completely lined with normal tracheal mucosa; none of the wire 'skeleton' was visible. There was some narrowing at the upper end of the reconstructed segment, but the lumen was perfectly adequate (*Fig.* 281).

The patient remained in normal health for the next twelve months and then, quite rapidly, her general condition began to deteriorate, the stridor returned, and she died (*Fig.* 282).

AT AUTOPSY.—There was a recurrence of the tumour in the right main bronchus and in the upper third of the trachea; seedling nodules were present in the right pleura. In the reconstructed portion the wire coil was completely embedded in the wall of the trachea, and the lumen, although narrowed to about 60 per cent of the area of the normal tracheal lumen, was lined with ciliated columnar epithelium. There were no metastases elsewhere. Both lungs showed terminal congestion, but no chronic infection.

In retrospect it would appear that in spite of the original biopsy report the tumour was a malignant cylindroma, and not a benign adenoma at all. Had the radical operation been performed in 1944 when the tumour was first excised, a cure might have resulted. The interest of this case lay in the demonstration that an extensive resection and reconstruction by the method described is possible, and that the functional result is satisfactory.

Case 2.—A female, aged 41, was admitted to the Unit in 1943 with a two-years' history of dyspnœa and discomfort in the right chest. Hæmoptysis had occurred on

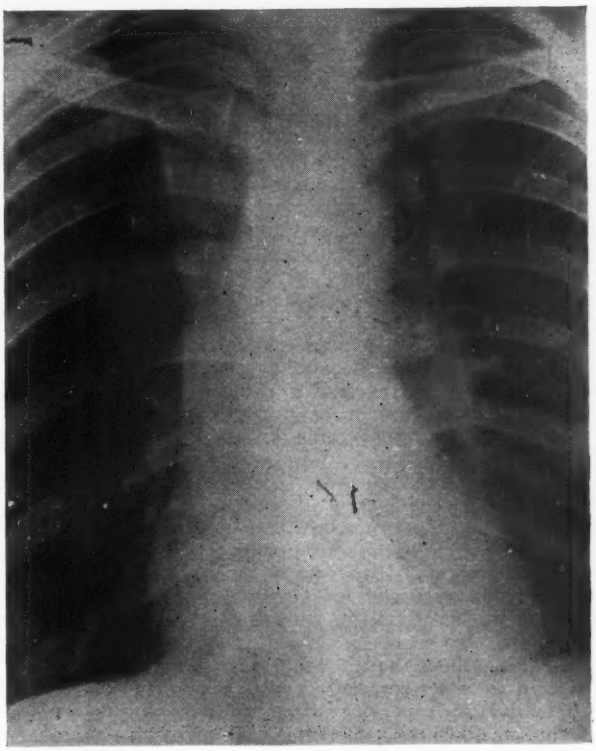

FIG. 283.—*Case* 2. Radiograph of chest showing atelectasis of azygos lobe at right apex.

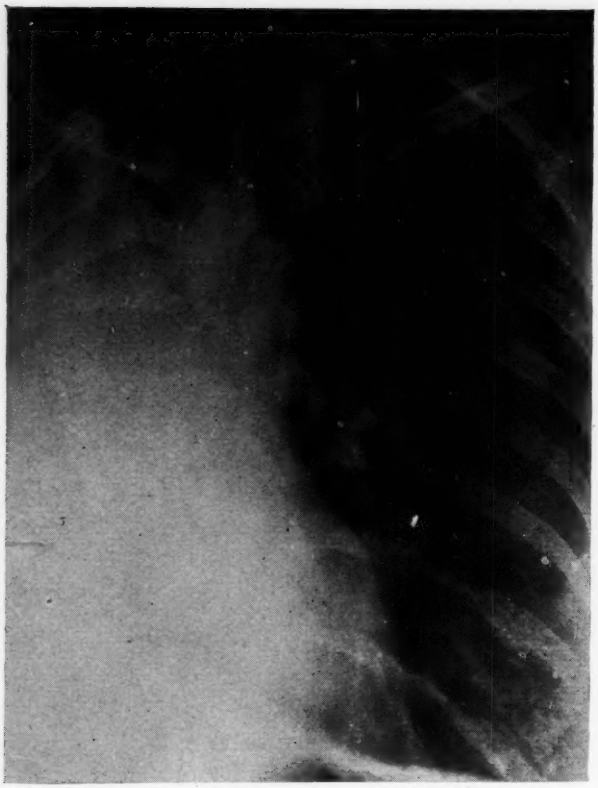

FIG. 284.—*Case* 2. Radiograph at time of second admission, six years after total right pneumonectomy.

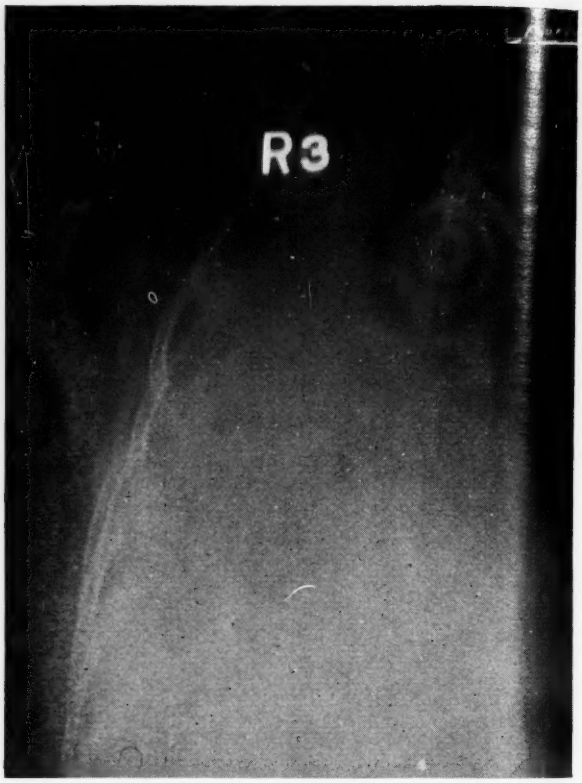

FIG. 285.—*Case* 2. Tomogram showing tumour almost completely obstructing the lower end of the cardia.

one occasion just prior to admission. Physical examination was essentially negative, but a radiograph of the chest suggested atelectasis of an azygos lobe at the apex of the right chest (*Fig.* 283).

Bronchoscopy revealed a tumour, with the macroscopical appearances of an adenoma, obstructing the right main bronchus, and growing from the anterior wall just proximal to the upper lobe orifice. A biopsy specimen was reported to show a benign adenoma of the bronchus.

AT OPERATION.—The tumour was found to extend up the right main bronchus and involve the lower end of the trachea for a short distance above the carina. An azygos lobe was present, and its bronchus was obstructed by the tumour. A right pneumonectomy was performed, and the tumour-bearing area of the trachea was resected. The defect was closed without difficulty. Convalescence was uneventful.

PROGRESS.—The patient remained well for six years, but was then re-admitted with stridor. (*Fig.* 284.)

Bronchoscopy revealed a recurrence of the tumour obstructing the lumen of the trachea, and extending upwards for a considerable distance above the carina. (*Fig.* 285.)

SECOND OPERATION.—A similar resection and reconstruction of the trachea as used in the first case was planned, but the procedure was somewhat complicated by the distortion of the trachea resulting from the previous pneumonectomy. The mediastinum was approached through the partially obliterated right pleural cavity; the tumour was found to involve most of the lower third of the trachea except the left wall, and was extending down the right wall of the left main bronchus. The tumour-bearing area was resected, leaving a very narrow strip of the left wall. It was not possible to remove all the tumour extending down the left main bronchus, and it was realized that only palliation could be hoped for; again it was obvious that the tumour was a malignant cylindroma,

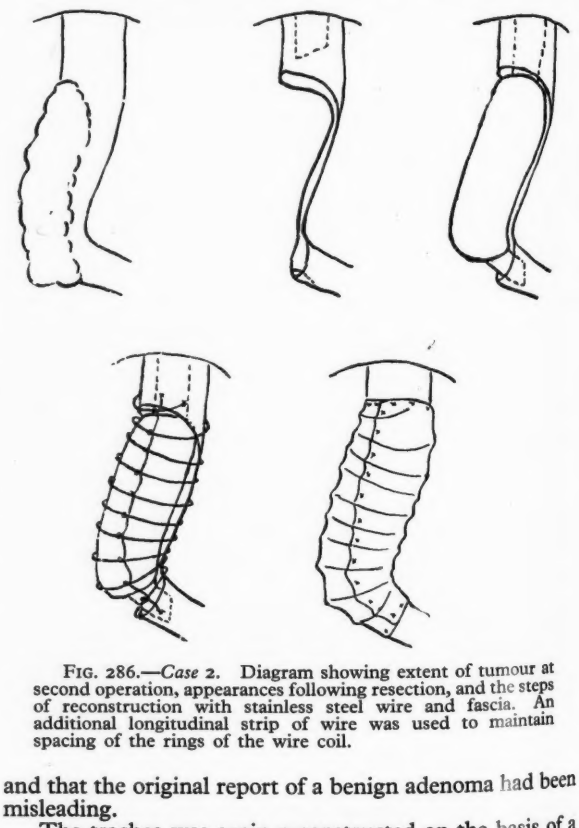

FIG. 286.—*Case* 2. Diagram showing extent of tumour at second operation, appearances following resection, and the steps of reconstruction with stainless steel wire and fascia. An additional longitudinal strip of wire was used to maintain spacing of the rings of the wire coil.

and that the original report of a benign adenoma had been misleading.

The trachea was again reconstructed on the basis of a stainless steel wire skeleton, as in the first case, with a

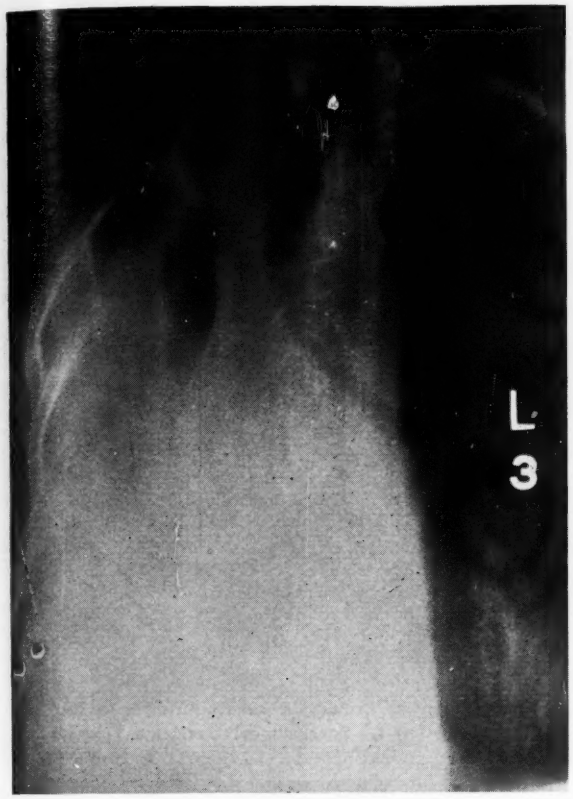

FIG. 287.—*Case* 2. Tomogram showing wire ' skeleton ' of the reconstructed trachea, and an adequate airway.

fascial graft, as shown in *Fig.* 286. An intratracheal tube with an unusually long cuff had been specially made to occlude the defect in the trachea while the reconstruction was proceeding.

PROGRESS.—Early convalescence was complicated by severe stridor and the production of mucopurulent sputum. On the fifth post-operative day the patient was bronchoscoped, and the appearances suggested that the 32-gauge wire used in the reconstruction was not sufficiently rigid and was collapsing. The bronchoscope was passed down through the reconstructed segment with immediate relief. Convalescence then proceeded smoothly but slight stridor persisted. Two months after operation the bronchoscopy was repeated. The lumen of the reconstructed segment was narrowed to about half normal, and a small granulomatous polyp was projecting in from the right wall. This was removed with biopsy forceps, and shown to contain no tumour tissue.

None of the wire skeleton was visible and the lumen appeared to be epithelialized, except for the region of the polyp. No biopsy of the mucosa could be obtained. A gum-elastic bougie was passed through the lumen without difficulty, and after this procedure the wheeze became almost imperceptible. The cough and expectoration have ceased and the patient is now leading a normal life again. (*Fig.* 287.)

It is too early to say how long this patient will survive before the tumour recurs, but the early functional result has been most encouraging, as in the first case where this method was employed.

DISCUSSION

Many methods of tracheal reconstruction will be tried before an entirely satisfactory technique is evolved. These two cases are presented to demonstrate that a physiologically, as well as an anatomically, adequate airway can be restored by at least one method that dispenses with an indwelling tube within the tracheal lumen, with its attendant risk of interference with the regeneration of the normal tracheal mucosa and its drainage mechanism.

In both cases a narrow strip of apparently normal tracheal wall was conserved to prevent retraction and further separation of the tracheal ends, and to provide a source from which regeneration of the ciliated mucosa could take place throughout the length of the reconstructed segment. This step could be justified by the tendency of these tumours to spread longitudinally up the trachea and not round the trachea till the later stages of the disease. But in an advanced tumour it would be unwise to conserve any tracheal wall in the region of the tumour.

Of interest in these cases was the absence of severe infection in the reconstructed trachea, and the survival of the fascial grafts. In the first case little penicillin was available and only two injections of 100,000 units were given during the post-operative period. The speed with which an extensive raw area was covered with regenerating ciliated tracheal mucosa inside the coils of the stainless steel wire skeleton was surprising.

SUMMARY

1. The problem of resection and reconstruction of the intrathoracic trachea in the treatment of primary tracheal neoplasms is discussed.
2. Recent experimental work is reviewed.
3. A new method of reconstruction is described.
4. Two cases treated by this method are reported.

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CARCINOMA OCCURRING IN THE SINUSES OF CHRONIC OSTEOMYELITIS

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MALIGNANT change associated with the sinuses of chronic osteomyelitis has long been recognized.

The first reported case of carcinoma of this type was by Hawkins, of London, in 1835, entitled "Cases of Warty Tumours in Cicatrices". From this date, until 1931, only 52 cases have been reported. To these, Benedict (1931) added 12, Henderson and Swart (1936) 5, Bereston and Ney (1941) 2, and, more recently, McNally and Dockerty (1949) have added a further 9 cases.

With the more general use of penicillin, and particularly streptomycin, in chronic osteomyelitis, this complication should become even less common.

We should like to add 3 cases to those mentioned above.

CASE REPORTS

Case 1.—H. T., a male aged 53, was admitted to this hospital on March 17, 1948. His original injury was a gunshot wound of the left thigh in 1917, with considerable soft tissue loss. There was no associated bony injury. Despite numerous Thiersch grafts to the affected area, it has been discharging for the past thirty-one years.

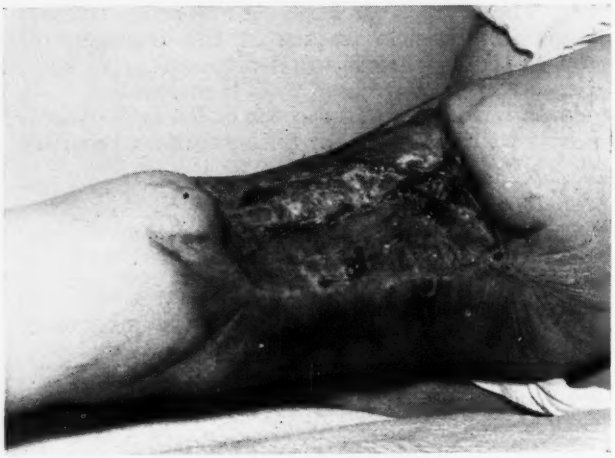

FIG. 288.—*Case* 1. Showing a large ulcer in the left thigh.

ON EXAMINATION.—There was a massive wound with marked loss of musculature extending from the lower third of the left thigh posterolaterally as far as the popliteal fossa. The entire lower third of this area had broken down, and there was a large ulcer present in the centre, with a profuse purulent discharge (*Fig.* 288). At the knee on the affected side there was 58° of movement. There was nothing of clinical significance in any other system.

TREATMENT.—Penicillin and bed rest were ordered in an attempt to clear up the discharge. To a certain extent this was successful, and after consultation with the plastic surgeon, closure of the defect by a large pedicle graft was decided upon. As a preliminary, the ulcer was excised on July 16, the raw area subsequently being grafted. However, due to profuse discharge from the region of the ulcer, the graft was a failure. Culture of this discharge gave an almost pure growth of *Staph. aureus* with some coliform bacilli.

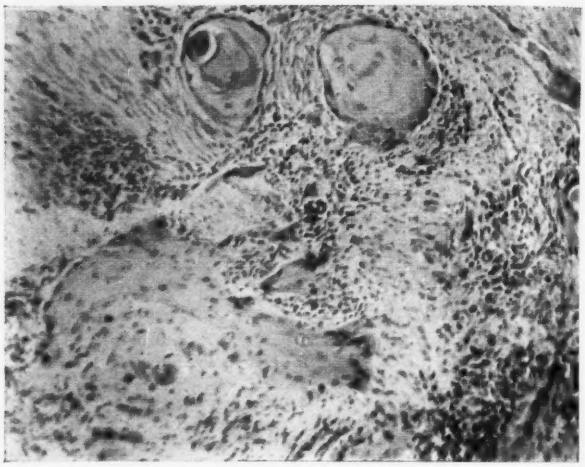

FIG. 289.—*Case* 1. Squamous-cell carcinoma. (× 460.)

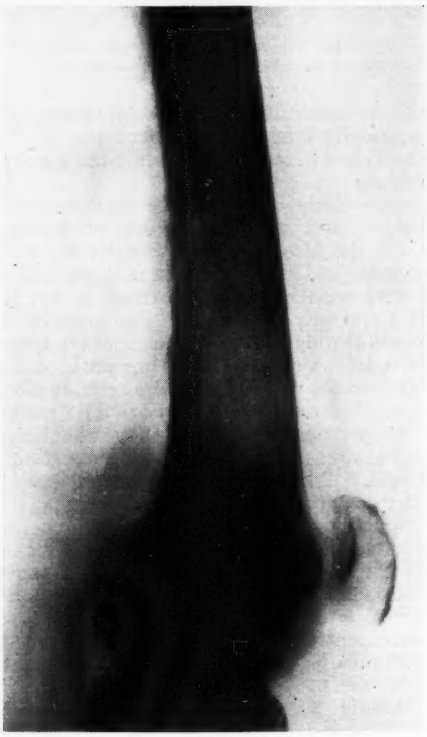

FIG. 290.—*Case* 1. Well-marked osteomyelitis on the posterolateral aspect of femur.

Biopsy report on the ulcer, dated Sept. 6, stated that the tissue was that of a squamous-cell carcinoma of low-grade malignancy (*Fig.* 289). Two weeks later, it was noted that one inguinal gland was palpable; this was removed for biopsy, and reported upon as being "benign inflammatory".

Following this, the entire tumour area was excised, including all the surrounding soft tissue down to the femur. During the procedure, the sciatic nerve was dissected back and some thickened perineurium and periosteum removed for section. The graft was then applied, and took extremely well, though it subsequently broke down over the site of the original ulcer. The biopsy report on both the periosteum and perineurium stated that they were invaded by squamous-cell carcinoma.

At this stage, radiographs of the pelvis, lumbar spine, and chest were taken without demonstrating any evidence of metastases. It was also noted that the lower two-thirds of the femur on its posterolateral aspect demonstrated well-marked osteomyelitis (*Fig.* 290).

As a result of this and the recurrence of the ulcer, high amputation was decided upon, and on April 12, 1949, the leg was disarticulated at the hip-joint. The post-operative course was uneventful. The wound healed completely, and there was no subsequent enlargement of the remaining inguinal glands. The pathologist's report on the disarticulated limb confirmed the presence of a well-differentiated squamous-cell carcinoma infiltrating the underlying muscles.

At the present date the patient is ambulant and awaiting limb-fitting.

Case 2.—J. H., a male aged 53, was admitted to this hospital on Sept. 15, 1949.

His original injury was a gunshot wound of the left thigh on March 21, 1918. He suffered a compound fracture of the left femur, which united in reasonable position with no shortening, though there was a small discharging sinus on the lateral side of the thigh.

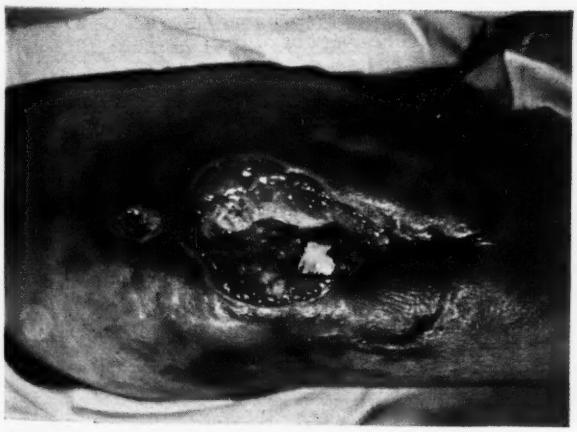

FIG. 291.—*Case* 2. Carcinoma occurring in sinus of left thigh.

Sequestrectomy was performed in October, 1919, and repeated on numerous occasions between then and July, 1921. The wound actually healed in June, 1924, when it was noted that there was a deep adherent scar on the lateral side of the left thigh, in which was a dry sinus. This continued to discharge at intervals, and in December, 1934, the wound broke down completely. He was treated for chronic osteomyelitis in a Winnett-Orr plaster-of-Paris cast with little improvement. The sinus continued to discharge, and in August, 1948, he was re-admitted to this hospital for guttering of the infected bone and immobilization in plaster. Despite this, his sinus continued to discharge foul-smelling purulent material. He was re-admitted on Sept. 15, 1949.

TREATMENT.—The bone was re-guttered. The discharge, however, persisted, and culture demonstrated an almost pure growth of *Staph. aureus*, with some *B. coli* organisms. A course of streptomycin was then given, with little clinical improvement, though as the fresh gutter wound began to heal it was noted that the sinus produced a cauliflower-like growth at its margins and from the depths (*Fig.* 291).

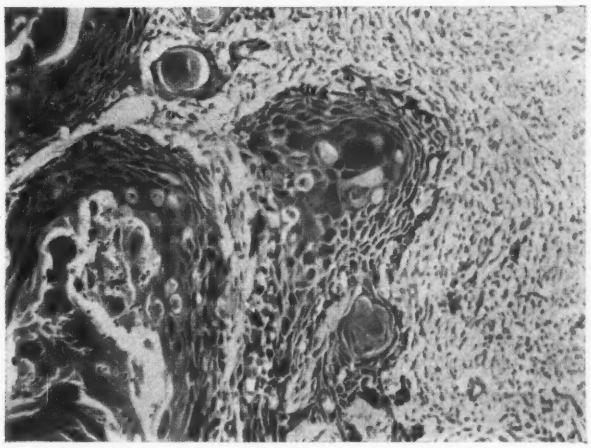

FIG. 292.—*Case* 2. Squamous-cell carcinoma. (× 460.)

Biopsy of this material was reported on as follows: " Strands of well-differentiated and keratinizing squamous-carcinoma cells, which are infiltrating all areas of the specimen sent for section " (*Fig.* 292).

FIG. 293.—*Case* 2. Osteomyelitis of left femur with sequestra and metallic foreign bodies.

X-ray examination of the patient's chest did not demonstrate any evidence of metastases, though radiography of his left femur demonstrated a well-marked osteomyelitis with the presence of sequestra and several minute metallic foreign bodies (*Fig.* 293).

Disarticulation at the hip-joint was performed on Feb. 3, 1950, an enlarged inguinal gland being removed at the same time.

The post-operative course was uneventful, and there was no subsequent enlargement of the remaining inguinal glands. The pathologist's report on the enlarged gland was as follows: "Section of the gland shows some follicular hyperplasia only. No evidence of any tumour deposit."

The patient is at present up in a wheel-chair, but had not yet attended for limb-fitting.

Case 3.—H. J., a male, aged 49, was admitted to this Hospital on Jan. 25, 1950.

This patient developed tuberculosis of the spine in 1920, the disease affecting the fifth, sixth, seventh, and eighth dorsal vertebræ. Within six months of the diagnosis being made, he became completely paraplegic, and suffered from both rectal and urinary incontinence. He was admitted to a sanatorium in 1920, and, during treatment, he states that he developed three sores, one over the sacrum, and one over either greater trochanter. In 1922, he began to recover from his paraplegia. This was accompanied by healing of the sores over the right greater trochanter and the sacrum. The sore on the

FIG. 294.—*Case* 3. Large carcinomatous ulcer of left thigh.

left hip almost closed up, but continued to discharge through a small sinus aperture. His spine was subsequently grafted, and he became ambulant.

He was admitted to this Hospital complaining of acute pain in the left thigh and a purulent discharging ulcer, around which he stated had formed a lot of "proud flesh." The discharge has been continuous for the past thirty years, and had become more profuse and foul-smelling six or seven weeks before admission.

ON EXAMINATION.—The patient was pale and cachectic, though there was no enlargement of the liver or spleen. A well-marked kyphosis was present in the mid-dorsal region, without any clinical evidence of reactivation of Pott's disease. Immediately beneath the left greater trochanter was a large ulcer approximately 3 in. by 2½ in., the edges of which were hidden by a firm cauliflower-like growth (*Fig.* 294). The discharge from the ulcer was purulent and foul-smelling. Culture revealed a heavy growth of Friedlander's bacillus and *Staph. aureus*. There was a 30° flexion deformity at the knee and a 45° flexion deformity at the left hip, associated with a large abscess on the posterolateral aspect of the left thigh.

Biopsy was performed on Feb. 2, the report being that the tissue was a low-grade squamous-cell carcinoma (*Fig.* 295).

X-rays of the dorsal spine demonstrated a healed spinal tuberculosis with a graft in situ, and the hip showed changes in the greater trochanter consistent with either a tuberculous or a low-grade pyogenic osteomyelitis (*Fig.* 296).

Owing to the flexion deformity, it was impossible to feel any inguinal glands in the groin.

TREATMENT.—Disarticulation through the hip joint was performed on Feb. 10. The post-operative course

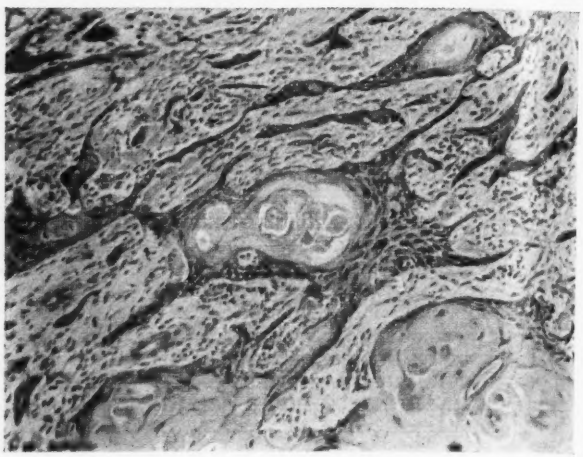

FIG. 295.—*Case* 3. Squamous-cell carcinoma. (× 460.)

was uneventful, except for small hæmatomata forming beneath the skin-flaps. No biopsy of the regional glands was performed, and no enlargement of these was noted. A pathological report on the disarticulated limb showed considerable infiltration around the ulcer site by squamous-cell carcinoma.

The patient is not yet out of bed.

FIG. 296.—*Case* 3. Low-grade osteomyelitis of greater trochanter.

DISCUSSION

It is most unusual to see three such cases within twelve months, even in a hospital where the surgical departments deal principally with the results of war

injuries. As far as can be ascertained, the three cases quoted are the only ones to have been seen in this hospital over a period of ten years, during which time a total of 354 amputations and re-amputations of the lower limb have been performed.

Henderson and Swart (1936), quoting 2396 cases of chronic osteomyelitis seen at the Mayo Clinic up to July 1, 1934, found that only 5 (0·2508 per cent) were associated with malignant change. Similarly, McNally and Dockerty (1949) found that only 9 (0·23 per cent) out of approximately 4000 cases had developed malignant change.

The reason for the rarity of carcinomatous change in the sinuses of chronic osteomyelitis cannot be due to one factor alone. Cohnheim's theory of chronic irritation, due to the discharge of pus on to the skin, may be to a certain extent responsible, but it does not explain the vast majority of cases which do not develop malignancy, some of which have had discharging sinuses of over thirty years' duration.

Other factors to be considered are age and diminished circulation. It is known that skin carcinomata are more frequent in elderly people. This may be due to a lessening of resistance of the skin in those past middle age, though there must be an additional constitutional factor, otherwise carcinoma would be much more common in the discharging sinuses of chronic osteomyelitis.

It is also known that scar tissue will automatically reduce circulation and resistance. In the cases referred to, apart from the presence of scar tissue, the site of malignant change is not one of deficient circulation, though this may be true of squamous-cell carcinomata occurring in the lower leg.

Clinically, recognition of carcinoma in such cases is difficult. Niebauer (1946) believes that a positive diagnosis can only be made by biopsy from a sufficiently large section of tissue. White and Weidman (1927), however, are of the opinion that a malignant condition microscopically is not necessarily a malignant condition clinically. We believe the truth lies between these two. In *Cases* 2 and 3, the diagnosis was obvious on clinical grounds, as will have been seen from the photographs. No pseudo-epitheliomatous hyperplasia quite resembles the exuberant growth of these cases, nor does it feel firm to the touch in the same way. In *Case* 1, the hard, rolled edge of the ulcer was not quite so obviously malignant. In all cases, biopsy is obviously necessary, though at no time was there any doubt in the pathological reports as to the nature of the tissue sectioned. All were squamous epitheliomata falling into Broder's Grade I class.

Enlargement of regional lymph-nodes was present in 2 cases, and a biopsy report was obtained for each. Neither showed the presence of tumour tissue, though both showed changes consistent with chronic inflammation; in this we are in agreement with Niebauer (1946), Henderson and Swart (1936), Bereston and Ney (1941), Blanco (1933), and others. There is no doubt that metastases are the exception. McNally and Dockerty (1949), report 2 cases of metastases in the regional glands, and Henderson and Swart, and Kirshbaum (1949), have added a further 2 cases, though in both of these the tumours were fibrosarcomata.

It is usually agreed that an increase in pain, discharge, hæmorrhage, and foul odour is responsible for these patients seeking further medical advice. The presence of a visible new growth arising from the sinus is also a definite cause. *Case* 1 of our series, who had been under constant observation, was the exception in that he had no visible tumour. The finding of a squamous-cell carcinoma on biopsy was the reason for more radical treatment. *Cases* 2 and 3 had all the features listed above, but in both it was the presence of a visible tumour which led to biopsy and subsequent radical treatment.

Amputation of the affected limb is universally regarded as the best line of treatment, though several authors follow this with post-operative deep X-ray therapy to the regional glands. Owing to this site of the tumours, all our cases were treated by disarticulation at the hip-joint. The use of deep X-ray therapy was not considered necessary on account of the negative pathology in the regional lymph-nodes. We have found that immediately the amputation wounds have healed, any enlarged regional glands subside. In all cases the prognosis in which a sufficiently high amputation has been performed appears to be satisfactory.

SUMMARY

Three cases of carcinoma occurring in the sinuses of chronic osteomyelitis are reported with the following conclusions :—

1. The condition occurs in males past middle age. In our series the average age has been 51·6 years, associated with a discharging sinus for an average of approximately thirty-one years.

2. Our findings make the commonest site to be the femur, though in the literature the tibia, femur, and foot are given in that order.

3. Enlargement of regional glands occurs in approximately two-thirds of all cases, but is usually due to chronic inflammation.

4. Profuse purulent discharge with foul odour occurs in all cases, though in only one (*Case* 3) had this become more noticeable.

5. Radical amputation above the affected site is the treatment of choice.

6. Prognosis after such treatment is satisfactory.

We should like to thank the Director-General of Medical Services, Ministry of Pensions, for permission to publish these cases; Mr. R. R. Green for the excellent clinical photographs; and Mr. J. B. Oldham for his advice and criticism.

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A REVIEW OF NEPHROMA AND TEN NEPHRECTOMIES IN 1949

By A. WILFRID ADAMS, Bristol

An incidence of 10 consecutive cases of renal neoplasm during 1949 in the Genito-Urinary Department at Bristol is somewhat exceptional and one of the reasons for making this communication. These tumours are uncommon, but fraught with great danger to the patient. There has been rather a dearth of literature dealing with the subject during this decade—possibly due to the war—and the situation is due for redress.

It is not one of those conditions chiefly of academic interest on account of its rarity and excusably relegated to the limbo by the overworked practitioner. On the other hand it is not inevitably in the doctor's mind—like rectal cancer—by reason of its frequency. It belongs to that intermediate class the detection of which is the hall-mark of the diligent discriminating doctor—uncommon but fell disease in which remedial benefits are in ratio to promptitude of treatment.

NOMENCLATURE

A precise standard classification of renal neoplasms which would enhance discussion on this topic has yet to emerge. An attempt in this direction is

Table I.—The Series of 10 Renal Tumours (1949)
(*In chronological order*)

Age and Sex	Clinical History and Radiography	Operation and Histology
	Tumour missed 18 Months prior: Surface suggested Tubercle	
G. T., male, 61	1947, hæmaturia starts 1948, recurs and monthly after 18 months ago kidney impalpable, prostate blamed 3 months ago kidney felt and cystoscopy negative I.V.P. (*Fig.* 297), right, nil Retrograde. Right, central space-filling lesion	March 18, 1949, right nephrectomy. Simulates tuberculous pyonephrosis, size of lemon; slight yellow elevations threaten rupture (*Fig.* 297). Pelvis of wine-glass form, ureter normal *Histology:* Renal adenocarcinoma Earlier I.V.P. might have saved mistaken prostatic diagnosis
	Four Years' History; Varicocele, Venous Permeation	
W. S., male, 67	1945, heavy hæmaturia for 2 days, otherwise well till recurred 2 months ago. Big, healthy, with lump left loin like enlarged kidney. Left varicocele remains on recumbency I.V.P. suggests tumour	May 6, 1949, left nephrectomy. Spinal anæsthesia. Tranquil *Histology:* Renal adenocarcinoma. Renal vein appeared full of clot but section taken shows that tumour cells have invaded lumen How much better if patient had had operation at onset 4 years prior March 20, 1950, feels and found radiantly well
	Pelvic Papilloma but Main Mass Hæmatoma	
C. H., female, 80	September, 1948, water first discoloured and sometimes since. Dull ache left loin May 31, 1949, started colic, hæmaturia, long clots. Lost weight ++. Condition fair but for waxy hue and tender, palpable kidney I.V.P., left shadow vague. Retrograde. Left pelvis distorted, upper calices absent	June 22, 1949, left nephrectomy. Kidney enlarged and 'set' as if in perinephritis *Histology:* Pyelonephritis. Papilloma of renal outlet shows degenerative changes but is simple. Naked eye (*Fig.* 299) mass mainly perinephric hæmatoma. Body of kidney mainly hæmonephrosis. Tumour at pelvic outlet is ¾ in. diam., stalked June 24, 1949, death from shock
	Calcified Shell suggests Cyst	
K. M., female, 62	April, 1949, hæmaturia started; occasionally right loin pain. Tender loin but no kidney felt, Giordano's sign positive Calcified arc left renal area I.V.P. (*Fig.* 300) expanded centrally as if by calcified cyst	July 16, 1949, left nephrectomy. Crenate surface of tumour (*Fig.* 300) *Histology:* Renal carcinoma Opaque outline of neoplasm—like shell of cyst July, 1950, review and investigation: Very well
	Two Years' History: No Tumour felt	
M. A., male, 59	2 years' hæmaturia, pain left loin, recurring quarterly Nil palpable Suspicious of large left kidney I.V.P. (*Fig.* 301), left suggests central lesion	Aug. 18, 1949, left nephrectomy. Transcostophrenic incision and incidental pleurotomy. Pedicle slipped out of ligature but transfusion not needed. Left pneumothorax resolved *Histology:* Renal carcinoma (*Fig.* 301)
	Sarcoma. Nephrocolectomy	
A. G. H., male, 54	Hæmaturia and lump left loin April 15, 1949, pain in left testis. Varicocele found. Suspensory bandage given. Pain recurred every 2 weeks, mild rigors, anorexia. Weight loss dubious. Urine had "brown powder" in it, and malodorous at times No pain but uneven lump left loin like coconut, almost fixed. Left varicocele present. Urine clear I.V.P. (*Fig.* 302), pelvis and calices displaced upwards and ureter medially as by smooth crescentic contour of ovoid mass	Aug. 24, 1949, left nephrocolectomy. Fey's approach made a major procedure manageable. Excision included thickened parietal peritoneum. Involved colon severed from growth and left in situ *pro tem.* Obstetric forceps wanted for delivering primary tumour (4¼ lb.) (*Fig.* 302). No outlying growth palpable. Via anterior laparotomy, 7 in. cancerous segment of descending colon removed and open ends re-united. Safety-valve cæcostomy. General condition fair Sept. 7, natural defæcation Sept. 17, discharged *Histology:* "Fibrosarcoma—probably arising from retroperitoneal tissue and involving kidney, colon, and peritoneal tissues." Naked-eye view suggests the reverse to the surgeon March 3, 1950, dead. Massive local recurrence

Table I.—THE SERIES OF 10 RENAL TUMOURS (1949), *continued*

AGE AND SEX	CLINICAL HISTORY AND RADIOGRAPHY	OPERATION AND HISTOLOGY
	Incidental Surgical Pleurisy	
M. A. S., female, 64	1 week left renal colic and hæmaturia. Much weight loss. Passed stones 30 years ago. Frail woman, lobulated mass left loin I.V.P. (*Fig.* 303), left central space-filling tumour	Aug. 31, 1949, left nephrectomy (*Fig.* 303). Incidental pleurotomy led to complications later Sept. 28, two pints sanguineous fluid withdrawn left chest. Malignant cells absent *Histology:* Carcinoma of the tubules. Neoplastic cells not seen in attached hilar glands May 18, 1950, review and investigation: satisfactory
	One Month's History: Glandular and Endovenous Deposits	
R. J. H., male, 64	6 weeks ago profuse hæmaturia and moderate ache in right loin for 3 days. Patient of fair nutrition but somewhat debilitated I.V.P. (*Fig.* 304 A) suggests right calcicosis, but shadow faint; left normal	Nov. 25, 1949, right nephrectomy. Transphrenic incision, exposing intact lower 2 in. of pleura (colour photograph, *Fig.* 304 C). Kidney enlarged to size of orange in upper region (*Fig.* 304 A). A few glands at base of pedicle removed. One suspected on the *inferior vena cava* proved to be *endovenous deposit*, measuring 1 × ¾ in. on lining of caval trunk. Dr. Curwen (radiotherapist) rejected radium but advised deep X-ray therapy, tantalum wire knot locating exact site. *Histology:* Renal carcinoma of clear-cell type with *secondary deposits in hilar glands* March, 1950, local recurrence in scar and depths
	Ten Days' History: Menacing Intravenous Extension	
W. E. W., male, 52	Dec. 3, 1949, hæmaturia, symptomless Somewhat debilitated man with lump like large Jaffa orange in left loin I.V.P. (*Fig.* 305), left rather attenuated representative pattern but inverted, like palm and fingers from side clawing central ball	Dec. 13, 1949, left nephrectomy. Delivery of enlarged kidney enclosed in perinephric and paranephric fat (*Fig.* 305) *Histology:* Rapidly growing renal carcinoma showing local renal metastases and invasion of renal vein
	Hæmaturia: Prostate removed prior instead of Causative Calcified Tumour	
A. B., male, 65	September, 1948, started profuse symptomless hæmaturia while in hospital for acute osteomyelitis of left tibia. Prostate blamed and removed when clot retention ensued Well till Dec. 19, 1949, bright hæmaturia and clots. Otherwise clinically normal Cystoscopy: bloody efflux from L.U.O. and no colour dye excreted. Opacities like ragged nucleus and partial halo over 12th rib (left) I.V.P. (*Fig.* 306), left, opacities about middle calix. Defective filling of pelvis and lower calices	Dec. 23, 1949, kidney slightly enlarged at nephrectomy; somewhat depressed central boss, smooth and pale. Renal pelvis like little goblet. No glands noted *Histology:* Transitional-celled malignant papilloma of kidney, partly calcified (*Fig.* 306) April 4, 1950, precautionary secondary ureterectomy *Histology*: normal June 5, 1950, reviewed: weight increasing

No case rejected during 1949. Seven cases alive and well, 1950.
Case 3.—Death from shock June 24, 1949. She was nigh *in extremis* prior to urgent operation.
Case 6.—Successful nephrocolectomy; massive recurrence, fatal March 3, 1950.
Case 8.—Local recurrence in scar, March, 1950.

made at the outset of this study by clearly defining significant clinical types.

The clinical title 'nephroma' is used for kidney tumours in general. They are sub-divided into:—

a. Parenchymal, adenocarcinoma.

b. Calico-pelvic, transitional-celled tumours classified like their congeners in the bladder.

Cystic conditions *in* and swellings *around* the kidney are merely mentioned as calling for differential diagnosis.

Is it not high time the misleading term 'hypernephroma' was discarded? What does the prefix 'hyper' connote? 'Super' perhaps! 'Nephroma' itself implies renal swelling. Admittedly, the histogenesis of the common type of renal cancer may be debatable, as fully discussed by Swan (1933); but this does not justify the perpetuation of a vulgarism. Hypernephroma may be euphonious; its etymology does not bear examination, and should it not die?

SUMMARIES OF THE CASES

THE 1949 GROUP

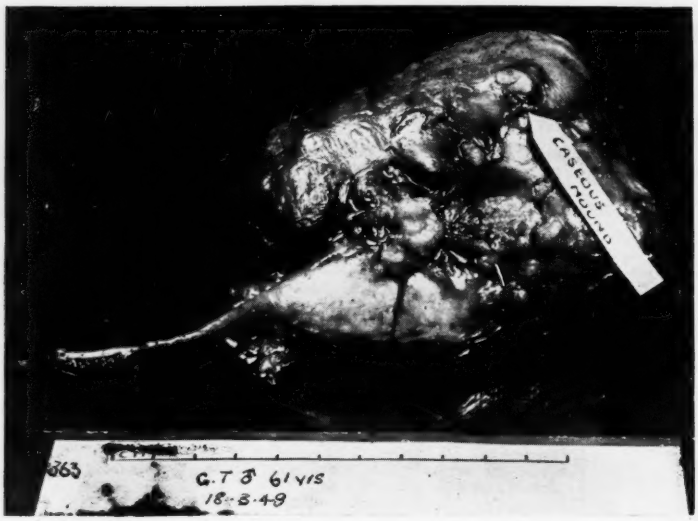
No case seen in 1949 was rejected. Of the 10 cases, 8 were left-sided. Only 1 died, C. H., a woman of 80 years, who was almost *in extremis* before operation. Of the 8 parenchymal carcinomas, already the fate of R. J. H. is sealed by recurrence in scar, although 7 are alive and well to date. "*What will be their state in five years hence?*" is the burning question of the prospective patient and his doctor. They must wait until 1954 for the answer and I hope the results may then be published and prove better than past figures lead us to expect.

A discussion of this group follows, focusing on salient features. But, obviously, such recent cases cannot afford useful evidence regarding long-term results. To provide more fully representative material with evidence on prognosis, some data from past experience of the disease have been added.

THE PRE-1949 SERIES

Among the 26 cases, 7 were found inoperable and died within a year of proved or presumptive adenocarcinoma. The fates of the 19 nephrectomies of known cytology are given briefly in *Table II* and *Fig.* 298.

In the adenocarcinoma the chart shows that 4 cases are now alive and well, while 1 did well for fourteen years, dying of hepatic cancer of uncertain origin. Some extenuation of the sombre figures is afforded by the facts that, first, as specified, 3 of the dead cases showed no evidence of residual renal cancer; secondly, a further 3 of the cases were so advanced that only a palliative nephrectomy was possible.



A

B

FIG. 297.—G. T., male, 61 years. A, Right kidney, external aspect like tubercle; B, Pyelogram, with kidney in section below.

Hanley's (1940) figures afford a useful comparison. He followed up all case records of renal neoplasm over a 5-year period in two general and one special genito-urinary hospitals. There were 27 cases, including 22 adenocarcinomas and 2 benign papillomas of pelvis. Six died within a week, 9 more within thirteen months, and 2 more within two years. Eight were alive, 2, 3, 6, 7, 8, 10, and 11 years after the operation.

In the *calico-pelvic epitheliomata* the chart is 'jet black' (*Fig.* 298); but 1 patient, coming late, survived four years; and again, 3 of the cases were already too advanced for more than palliative surgery.

PROGNOSIS

In the common type of nephroma, adenocarcinoma, the doctor may reasonably expect a 20 per cent 10-year cure rate. Far earlier diagnosis is attainable, as stressed by Hinman (1917), and, if made actual, prospects of the patient would rise to nearer 40 per cent, given good surgery.

The calico-pelvic epitheliomata mostly come in a late phase and operation rarely does more than ease the patient's last year. Scholl and Foulds (1924) report 2 cases of squamous carcinoma and remark on the very fatal nature of this type. Often it is secondary to long-neglected inflammatory

Table II.—POST-OPERATIVE HISTORY OF 19 NEPHROMATA (PRE-1949)
(*Tabulated in post-operative ages, and of proved cytology*)

	1ST MONTH	YEARS									
		1	2	3	4	5–11	12	13, 14	15	16	17
14 cases, parenchymal adenocarcinoma	**J. C.*** (*Fig.* 317) **L. C.** **A. W.‡** **J. P.*** (*Fig.* 307)	**H. B.** **C. H.** **M. M.** **S. L. W.*†**		**J. M.‡** H. V. F. (*Fig.* 316)	A. B. (*Fig.* 309)		E. D. (*Fig.* 308)		**N. W. M.** (*Fig.* 310)	L. H. (*Fig.* 311)	
5 cases, calico-pelvic carcinoma	**M. A. F.*** (*Fig.* 312)	**E. C. E.*** **M. S.** **J. T.‡** (*Fig.* 314)			**T. B. C.*** (*Fig.* 313)						
19 cases, total											

Cases in heavy type died, e.g., **J. C.**

* *Advanced Cases:* **J. C.**, obscure pyrexia. **J. P.**, died of pulmonary infarction; no residual cancer.
M. A. F., massive calculi.
T. B. C., 3-lb. tumour.
† *Nephrocolectomy:* **S. L. W.**, colon damaged.
‡ *Specific Cases:* **A. W.**, died shortly after operation, large metastasis base of lung.
J. T., 6 m. after nephrectomy; total gastrectomy for cancer killed him; no recurrence noted.
J. M., cardiac death in hospital, hypertension; no post-mortem.

trouble. This tragic situation teaches that timely intervention on inflammatory precursors would enable surgery to *prevent* half these calico-pelvic growths.

From the 1949 series and previous material, evidence has been culled and, for its didactic value, considered under leading symptoms.

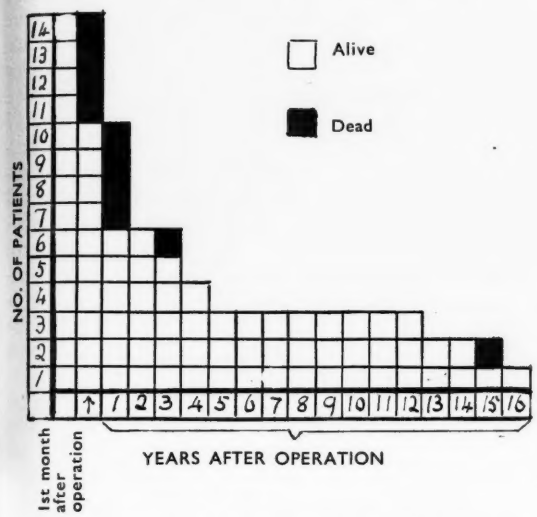


FIG. 298.—Graph of pre-1949 cases, showing survivals.

HÆMATURIA

There are three classical symptoms of nephroma—pain, lump, and hæmaturia, and the greatest of these is hæmaturia. In the 1949 group it occurred at some time during the illness of all 10. It was virtually the sole symptoms at the onset in 7. The average time between the first hæmaturia and nephrectomy was thirteen months and the longest was four years. With the large *sarcoma* of A. G. H. (*Fig.* 302) stale blood started mildly some weeks after the illness commenced. In the renal papilloma C. H. (*Fig.* 299), the patient had noted her urine occasionally "discoloured" for nine months before the final heavy hæmaturia.

Renal colic from ureteric clots occurred in two 1949 cases. Although vesical retention threatened others, it did not call for a catheter. Cutler (1924) found clot blockage compelled catheterization in 5 out of 32 histologically-proven nephromas.

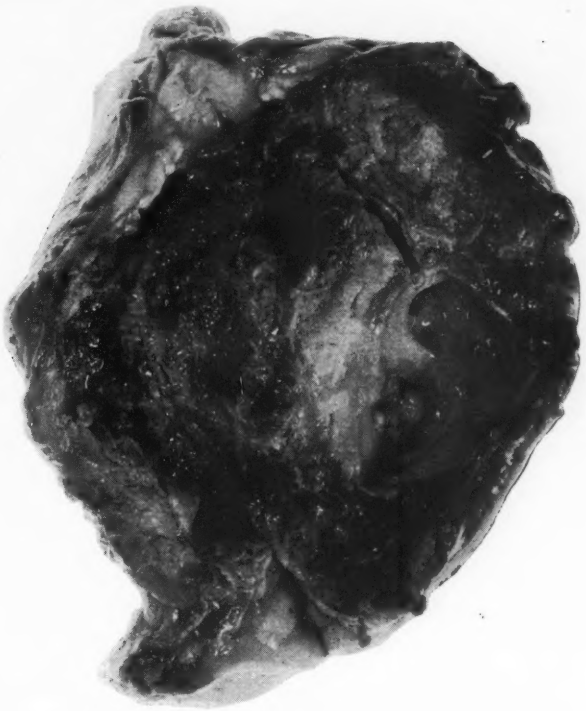
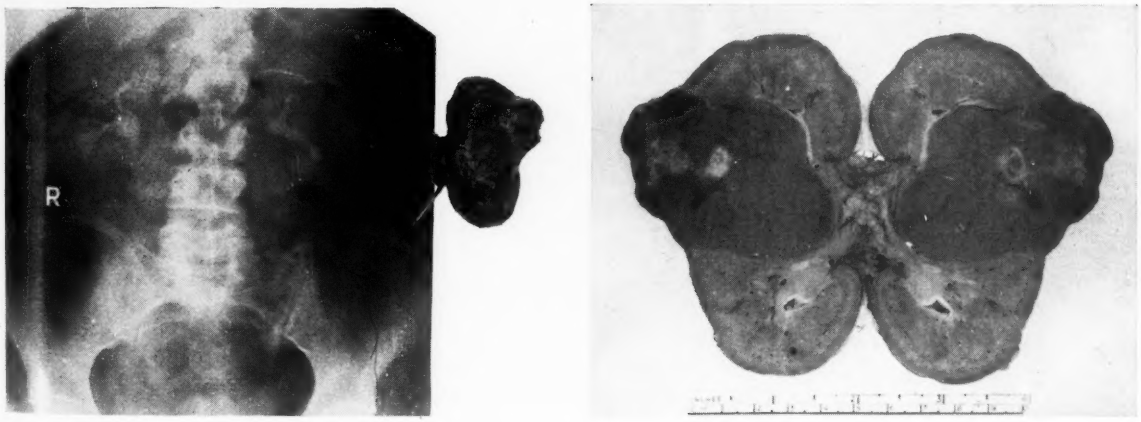


FIG. 299.—C. H., female, 80 years. Operation specimen of kidney showing a small benign papillomatous growth of the renal pelvis, but bulk of 'tumour' consists of resulting organized perinephric hæmatoma. (× ⅔.)



A B

FIG. 300.—K. M., female, 62 years. A, Calcified shell in radiograph of adenocarcinoma; B, Kidney on section.

It is common knowledge that distinctive details in the type of bleeding may point to a particular part of the tract as the source of hæmaturia, and tenderness or underlying swelling suggest aetiology; but suffice it here to insist that we respond to this serious portent by relentless diagnostic pursuit until the surgical or medical cause is clear.

Management.—Because it is the chief distress signal of the victim of renal neoplasm, it is impossible to exaggerate our duty to the patient attacked with hæmaturia. Swan (1933) urged the profession

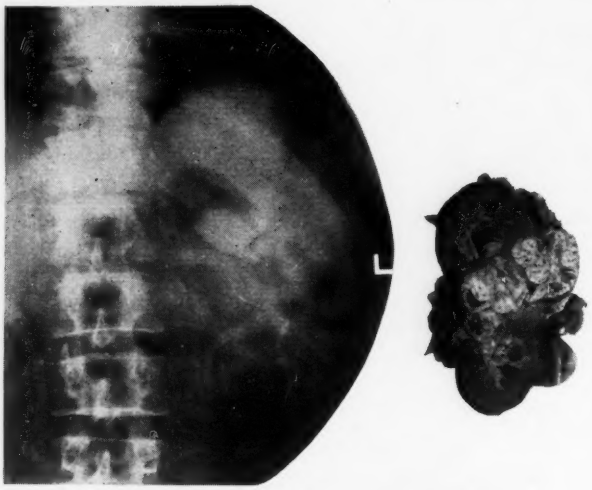
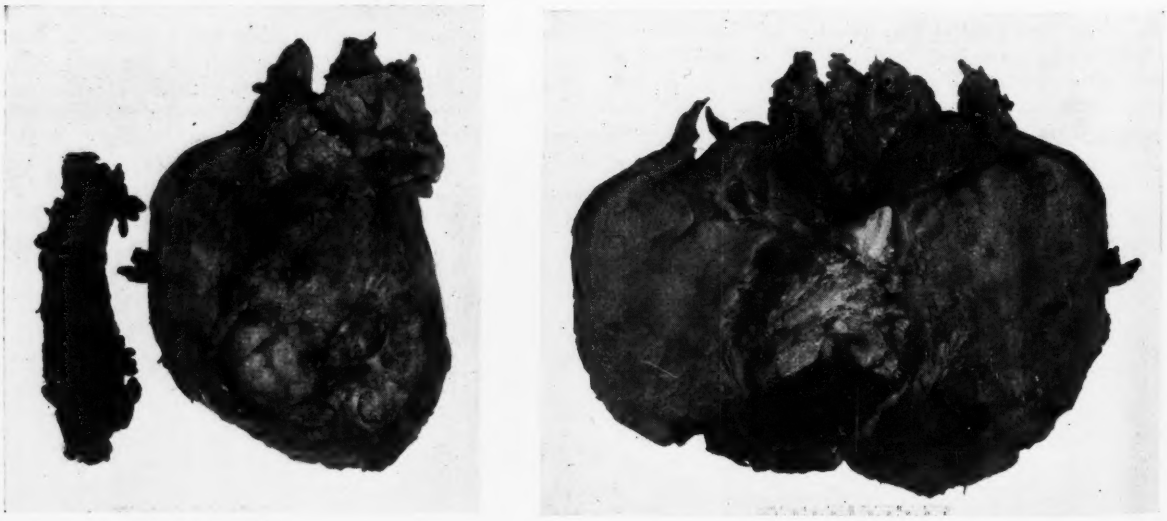


FIG. 301.—M.A., male, 59 years. Adenocarcinoma; pyelogram suggests central tumour, section shows twin foci.

to take a more serious view of hæmaturia, as did Simpson (1934). "Facts", says Hinman (1917), "indicate the lost opportunity in making an early diagnosis. At the time of operation, presumably of diagnosis also, less than 10 per cent had one symptom only, while in 42 per cent (709 cases of eight surgeons) hæmaturia had been the initial symptom, in 32 per cent (of 643 cases) pain, and in 18·5 per cent (of 611 cases) tumour." It should rank as a clinical emergency and the profession remain restive until the facilities for immediate investigation are both ample and competent. Only when the cystoscopy is done *during* hæmaturia can it give the *vital clue* as to *which kidney* is the source.

Cystoscopy most commonly discloses a vesical wart. When neither this nor stone is seen, one is inclined—in a male—to blame bleeding on latent prostatic enlargement. Such a facile conclusion must be sternly resisted until it is fully confirmed and upper tract alternatives are excluded. Variation between the two ureteric effluxes is watched for after intravenous indigo-carmine. Resort to excretory pyelography may reveal gross deformity, or mere suspicion may invite clarification by retrograde pyelography. Suppose, however, as often holds true, all these and urinary tests for tubercle prove negative, does this end surgical responsibility? Experience answers with a categorical 'no'. Illuminating as are the penetrating studies of the radiodiagnostician, a neoplasm may grow and bleed without encroaching appreciably on the pyelographic pattern. Debenham (1933) gave a valuable contribution in his study of 742 cases. My experience, however, suggests that his concluding words regarding unexplained hæmaturia are rather too rosy—"The prognosis is good, if nothing abnormal can be found on full urological investigation."

The 'Follow-up'.—This must be axiomatic because an upper urinary source of hæmaturia may give no appreciable pyelographic deformity for months or even a year or two. Once the patient recovers from a startling show of blood which is quickly over, and feels otherwise well, he is all too prone to make light of brief recurrences and, especially so, if after initial investigation he is told there is nothing serious afoot. In a negative case, three-monthly detective urography is due for two years at least.

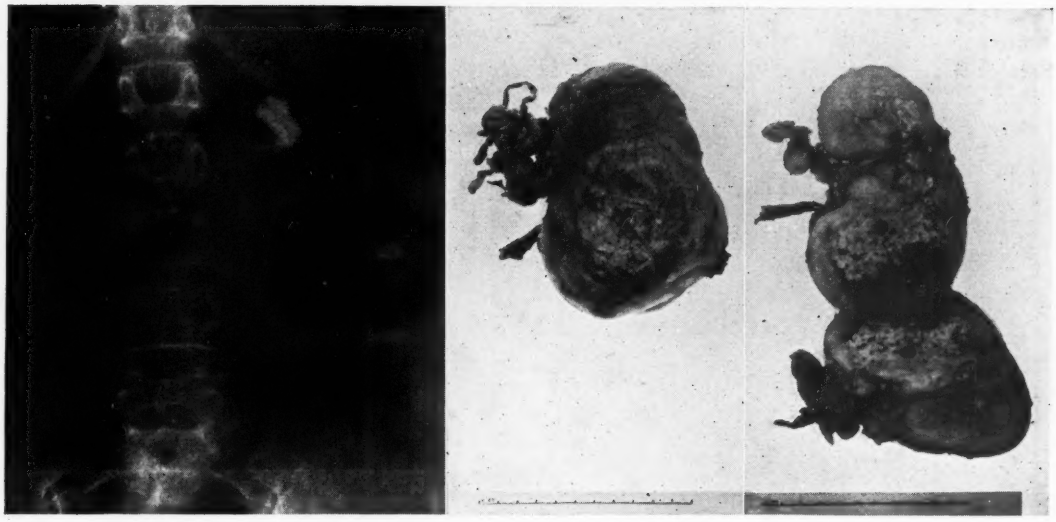


A B

FIG. 302.—A. G. H., male, 54 years. Sarcoma of left kidney; weight 4¼ lb. A, Showing tumour and invaded colon; B, Section of kidney.

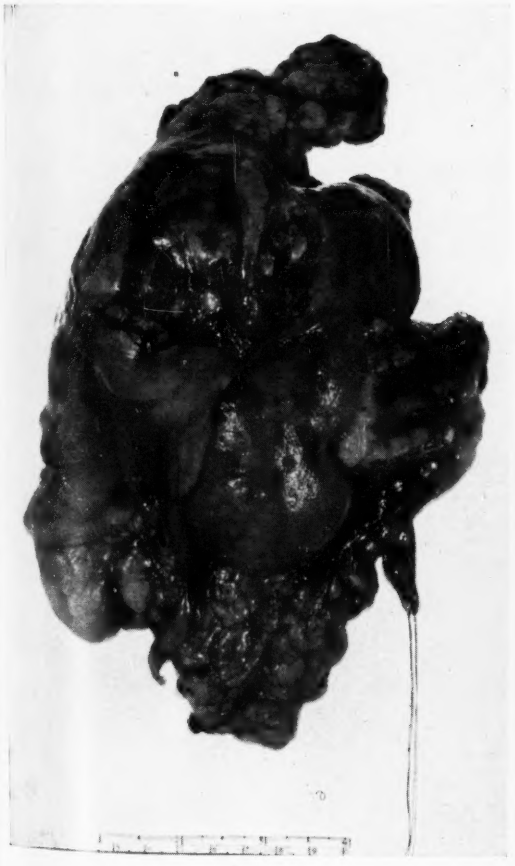
MISTAKES POINT THE MORAL

The 'Idiopathic Illusion'.—J. H. F., male, 60 years, May, 31, 1944, came in with severe symptomless hæmaturia. He looked well and cystoscopic tests gave no clue. On intravenous pyelography, pelves and calices could just be descried, right fainter than left.

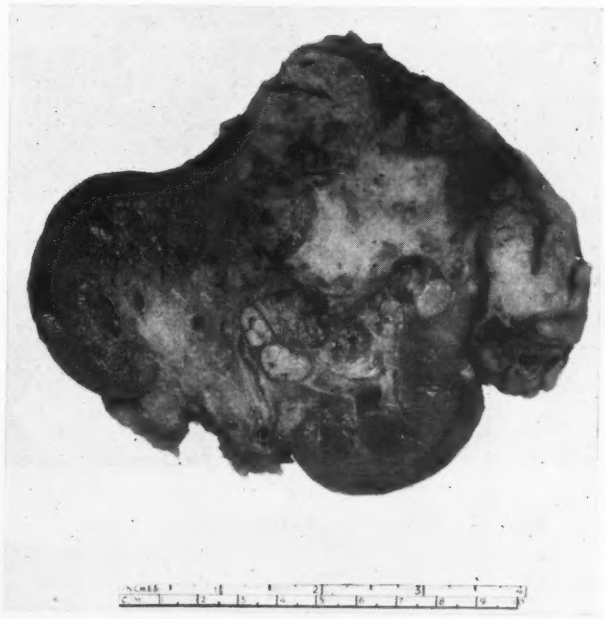


A B C

FIG. 303.—M. A. S., female, 64 years. Adenocarcinoma. A Pyelographic defect due to tumour of spongy texture. B, Operation specimen, showing a large hypernephroma. There are hilar glands attached to the specimen. C, The kidney in section. Histology shows the *tumour* to be composed of characteristic large cells having clear cytoplasm. A section of the *glands* show large cells with clear cytoplasm lining the sinuses. These cells are littoral cells and not neoplastic deposits.



A

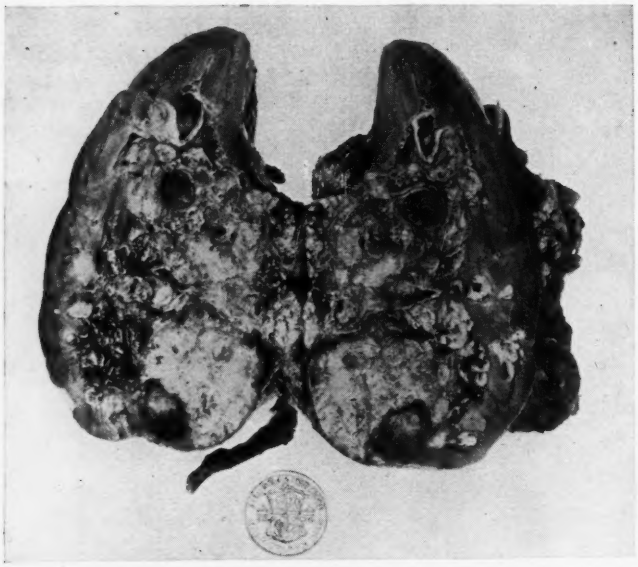


B

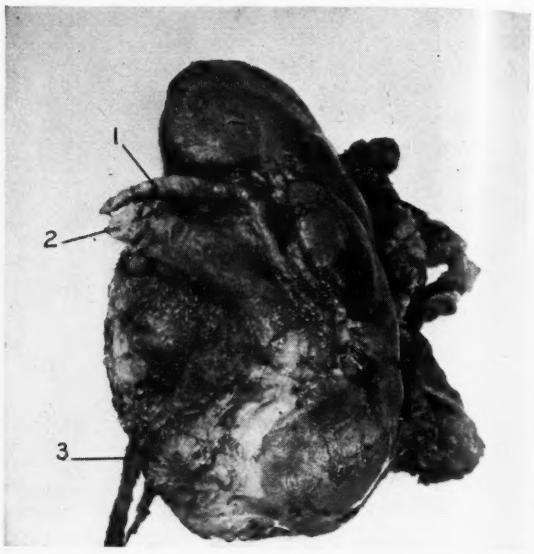
C

D

FIG. 304.—R. J. H., male, 64 years. Adenocarcinoma. A, B, Shows exterior and sectional view of florid tumour with vena caval implant. C, Exposing kidney by Fey's incision. Intact pleural membrane seen above diaphragm. D, Access to hilar lymphatics after nephrectomy by Fey's incision.



A



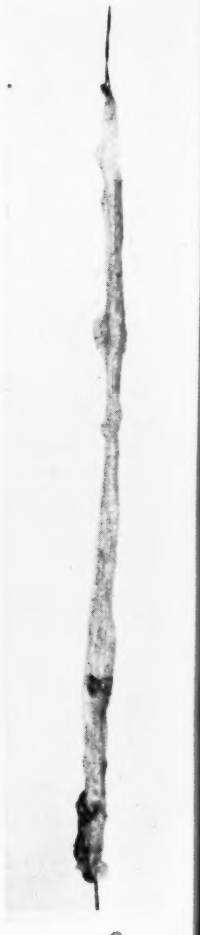
B

FIG. 305.—W. E. W., male, 52 years. Adenocarcinoma. Massive invasion seen in sectional (A) and external (B) views of kidney (1, Artery; 2, Vein with growth protruding; 3, Ureter bent forward by post-medial neoplasm). C, Pyelogram showing calices directed inwards from lateral pelvis.

C

A

B



C

FIG. 306.—A. B. (1949), male, 65 years. Transitional-celled calico-pelvic epithelioma. Calcified focus indicated in tumour section (A, × ½) and as ragged nucleus and broken halo in pyelogram (B); C, Specimen from precautionary ureterectomy, biopsy normal.

Precautionary right retrograde pyelogram (*Fig.* 315 A) dispelled all thought of tumour and he went home. I next saw him on Nov. 16. It was a ghastly shock to find an inoperable mass in the right hypochondrium and 'stark clear' renal cancer by retrograde pyelography (*Fig.* 315B). He died at home a fortnight later. This is an awful lesson to any about to accept a diagnosis of 'idiopathic' hæmaturia.

advised against surgery in a frail subject. It continued and brought him to me in 1943. He was rather a physical wreck and carried a large hard lump in his right loin. On removal (*Fig.* 313) it weighed 3 lb., yet he did busy war-work almost till his death from recurrences four years' later.

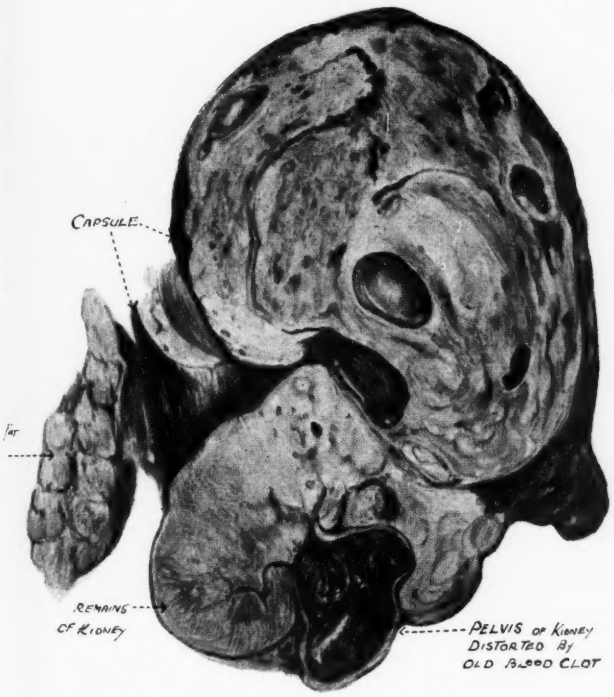
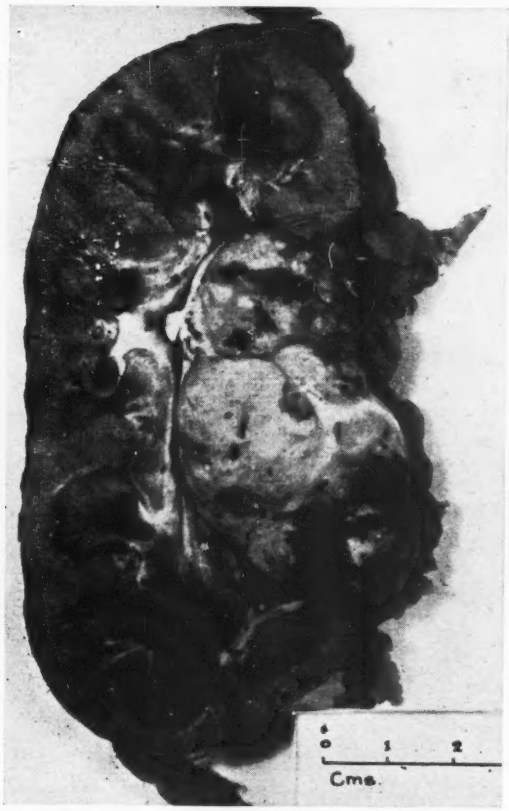


FIG. 307.—J. P. Shows adenocarcinoma, clot in pelvis, and large perirenal extension.



B

The Doctor's Timidity.—In 1939, T. B. C., male, 69 years, started hæmaturia. His doctor

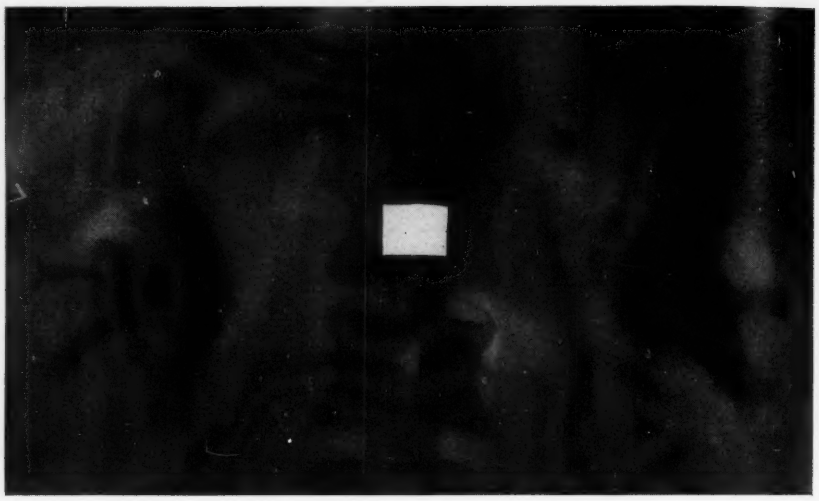
A

C

FIG. 308.—E. D. Shows pyelogram (A), and specimen (B) of adenocarcinoma in 1939 and photograph of the patient (C) in 1949.

FIG. 309.—A. B. (Pre-1949) Shows section of kidney composed of a compact congeries of yellow lobules—the usual adenocarcinoma renalis.

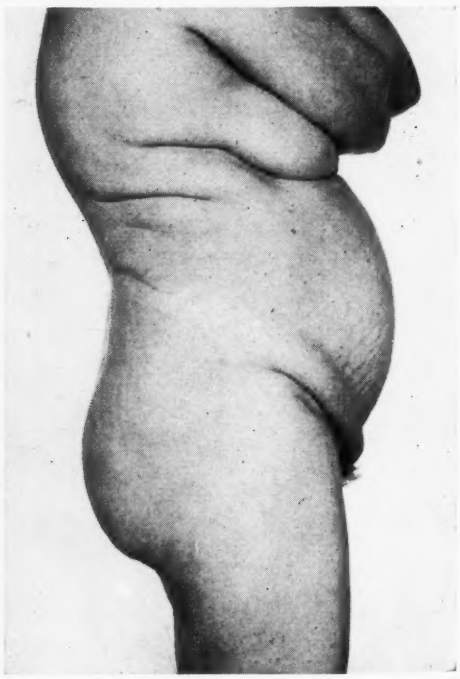
A



B

FIG. 310.—N. W. M. Hypernephroma of right kidney. A, Specimen; B, Pyelogram.

A



B

FIG. 311.—L. H. A, Shows kidney removed 1934; B, Photograph of patient's flank in 1950, sixteen years after nephrectomy for cancer.

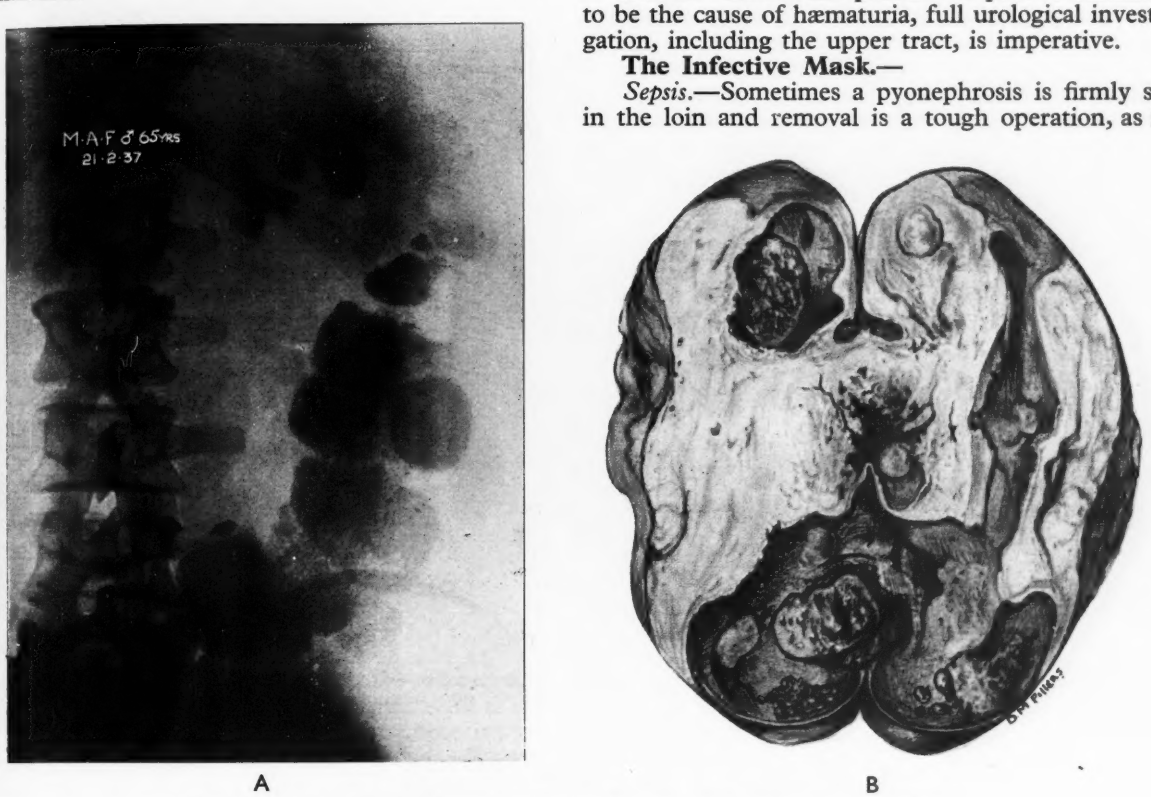
Other local lumps, like unto nephroma, are "perirenal tumours and cystic formations of the kidney" (Hinman, 1917), and these may cause hæmaturia.

The Prostatic 'Decoy'.—In G. T., and A. B. (1949) the prostate was mistakenly blamed for hæmaturia arising from kidney tumours (*see above*).

Moral: Unless the prostate is proved infallibly to be the cause of hæmaturia, full urological investigation, including the upper tract, is imperative.

The Infective Mask.—

Sepsis.—Sometimes a pyonephrosis is firmly set in the loin and removal is a tough operation, as in



A B

FIG. 312.—M. A. F. A, Massive nephrolithiasis (left); B, The specimen in section.

FIG. 313.—T. B. C., male, 69 years. Shows the exterior and sectional views of calico-pelvic epithelioma. (× ⅜.)

M. S. (pre-1949). So I was less disappointed on having to re-operate twice for persistent sinus without finding any obvious cause. Necropsy gave this poor subject. The patient had started hæmaturia in 1947. A second attack occurred in 1948, for which I cystoscoped him and blamed the prostate. Pyelography was omitted. Although monthly hæmorrhage had continued, he did not return to my ken until 1949 when, *at this late stage*, I removed what proved to be a cancerous kidney.

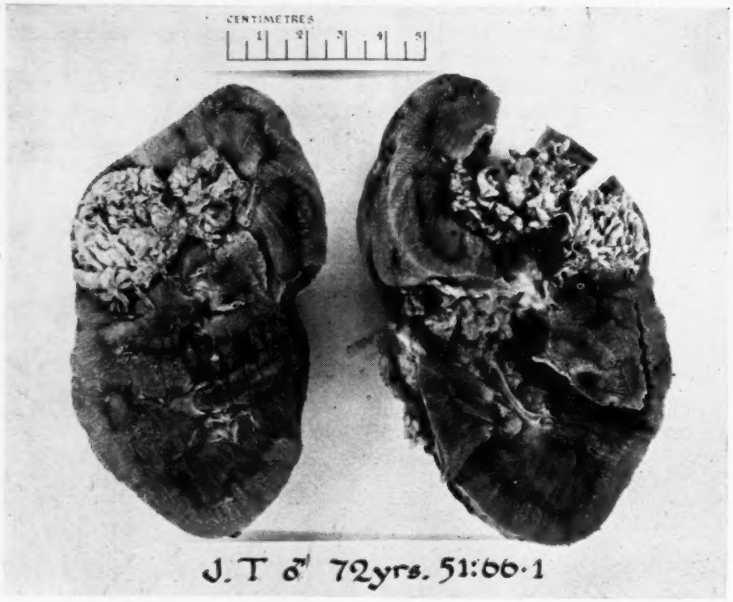


FIG. 314.—J. T. Shows calico-pelvic transitional-celled epithelioma (pre-1949). (×½.)

P.U.O.—Virus infection, etc., may be blamed when the patient defies diagnosis while merely deteriorating during some months with an obscure febricula and no urinary symptoms. Suddenly, the doctor is surprised to find a tumour lurking in the loin. Prognosis is poor, too, judging by my private patients, J. C., 64 years (pre-1949), who died four hours after nephrectomy for adenocarcinoma (*Fig.* 317), and E. C. E., who had languished for eleven months prior to diagnosis. After nephrectomy, the transitional-celled epithelioma soon recurred, fatally.

Syphilis.—A gummatous kidney might have been inferred during the operation on C. H., owing to the leathery consistency and fixity of the perinephric tissues. The reverse is much likelier—gumma mistaken for cancer.

Calculi and Calcification confuse Diagnosis.—Instances of renal opacities confusing the issue are provided by my cases. In K. M. (1949) the cancerous swelling was thought to be a calcified cyst (*Fig.* 300), while in A. B. (1949) a small calcified kidney in H. V. F. (pre-1949) is reminiscent of carbuncle (*Fig.* 316).

FIG. 315.—J. H. F., male, 60 years. Case of hæmaturia. Shows right pyelogram—normal on May 11, 1944 (A), and grossly invaded Nov. 16, 1944 (B).

Tubercle.—G. T. (1949). The caseous and distended aspect of the exposed kidney (*Fig.* 297) led me to a tentative operation diagnosis of tubercle in me the clue, revealing scirrhous cancer arising from renal pelvis. Was this secondary to chronic renal stasis, or the cause of it? The latter is suggested by the brief history. The external aspect of the focus (*Fig.* 309) was not duly recognized as a portent of cancer. In the case of M. A. F., already reported by Adams (1937), squamous cancer of the *uninfected* renal pelvis complicated massive calculi (*Fig.* 312) with thirty years' history of hæmaturia. In M. S.

(pre-1949) the diagnosis remained calculous pyonephrosis until post-mortem after the third operation for the disease in twelve months.

Varicocele (Left).—This was found twice at the primary interview—W. S. and A. G. H. It persists on recumbency and only occurs on the left where the union of spermatic and renal veins is

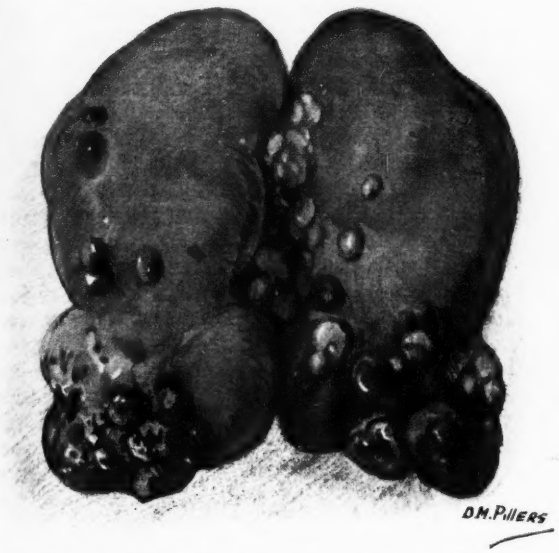


FIG. 316.—H. V. F. Shows adenocarcinoma of kidney simulating carbuncle (May 3, 1947). Patient well until suspected recurrence R. loin, Spring, 1950.

liable to implication. If there is no extension of growth into the vein, but merely pressure upon it, relief follows ablation of the kidney tumour, as in my two cases.

Precursory Metastases mislead.—Another paradox is the appearance of a secondary focus, such as a wen on head or spontaneous fracture, while the renal primary remains silent. In 1 of the 7 (pre-1949) inoperable patients a left clavicle had been removed for neoplasm a year before the onset of hæmaturia, for which I was invoked.

Moral: Not only is naked-eye examination of removed tissues needed, but routine histology in all except the indisputable diagnoses.

Sarcoma.—Judd and Donald (1932) found a 5 per cent incidence of sarcoma in 570 renal tumours. My only case (A. G. H., 1949) showed local recurrence in three months and was dead by six months. Herman and Greene (1932) reported 2 cases illustrating the exceedingly malignant character of renal sarcoma in adults.

TECHNIQUE OF OPERATION

A. Access—The Incision.—Exposure through the fleshy flank means that the surgeon approaches the kidney obliquely, hampered by the overhanging ribs. To avoid this *Fey's route* (1925) became favoured in the 1949 cases. He divides the diaphragm directly over the renal pedicle and the regional lymph-glands, like a builder who goes direct through the roof on to a fault and not up under the eaves. Where it is a case of eradicating deadly disease, easy access fortifies the surgeon and gives him a most welcome feeling of command over the situation (*Fig.* 304 A). Partial removal of the eleventh rib facilitates retraction.

Swan (1933) claims that the alternative transperitoneal approach to nephrectomy facilitates the inclusion *en bloc* of the extensive fringe composed of fatty fascia, lymph-glands, and suprarenal, and gives early access to the engorged venous channels. Sugar (1930) remarks on the disadvantages and supports his claim for the customary retroperitoneal lumbar route by recording successful extirpation of kidney and involved colon.

Accidental *pleurotomy* occurred in 3 cases. Although distress was inconspicuous, it adds risks which are avoidable in the majority. Two aspirations of the pleural effusion were necessitated in the case of M. A. S. (1949). Since following the advice of my colleague, Mr. Melville Capper, that the pleura (*Fig.* 304 B) descends less obtrusively with the patient rolled only halfway on to side and the table tilted slightly into Trendelenburg's position, I have not incurred pneumothorax.

In the case of M. A. (1949), through a technical fault the ligature slipped off the pedicle. Ugly scenes amid serious blood-loss are apt to mark such occasions; but I was able to retrieve the situation, thanks to the vascular stalk being centrally sited in the gaping wound. Digital control was easy, forceps and ligature following with calm deliberation.

Again, in the case of A. G. H. (1949), wherein a large tumour had to be freed, involving its relations to pancreas, colon (*Fig.* 302), etc., complicated surgery was done with acceptable assurance under comfortable exposure.

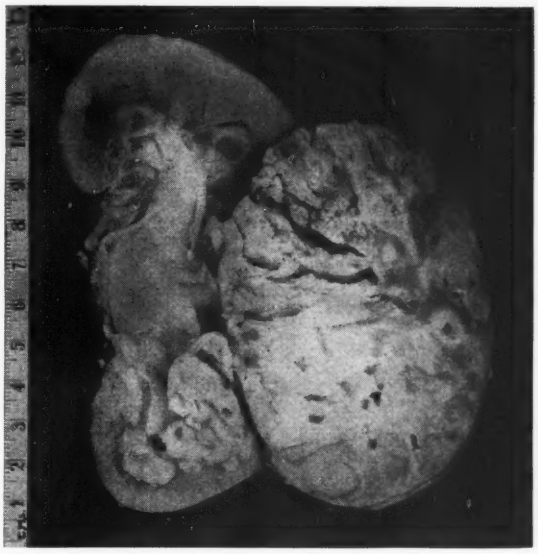


FIG. 317.—J. C., male, 64 years. Adenocarcinoma. Photo of specimen.

B. Range of Operation—The Lethal Venous Effluent.—There were cases during 1949 illustrating the sinister significance of the renal vein in spread of nephroma.

1. The specimen of W. S. (1949) shows growth extending to within a centimetre of the sectioned mouth of the renal vein.

2. In W. E. W. (1949) a long, large, renal vein was found clear of growth where divided about 2 in. from the hilum. An hour later I re-examined the specimen and, to my horror, a tongue of growth, like a yellow slug, projected a centimetre from the mouth of the divided vein which had retracted (*Fig.* 305).

3. The final shock in this respect was provided by R. J. H. (1949). After the main removal I felt an area like an almond on the inferior vena cava above the junction of the renal vein. The truth was worse than I guessed, for on re-examination the deposit of growth was actually on the lining of the venous trunk. Intervention was prohibitive. Nothing short of segmental resection would have been wide of the focus and this would have involved the opposite renal vein! I was too late, despite a history of only one week. The site was precisely marked by the insertion of a metal suture at the suggestion of my registrar—Mr. F. R. Hurford—as a target for radiotherapy.

Priestly and Walters (1933) report 2 cases in which carcinomatous outgrowth into the vena cava was extracted and the venous trunk successfully sutured.

The distinctive and dominant importance of the venous exit deserves more prominence in both the pathology and surgery of cancer of the kidney. My cases exemplify the truth of the assertion that in nephrectomy for tumour our *main contention is with the renal vein.* It is very large, short, and quickly conveys its contents to the caval trunk. Cancerous emboli can easily stream along it into the circulation.

Although jeopardizing the patient's life in this glaring manner, the renal vein puts into the surgeon's hands unusually *effective power of controlling the spread* of cancer because—aside from an occasional polar vein—it is the sole effluent. The surgeon has only to clamp down on that single conduit quickly to render effective aid to his patient. Via the solitary vein, as in my operative findings, cancer extends *by continuity, adjacent implantation, and distant embolism.*

The Surgeon's Aim.—

1. Early juxtacaval closure of the vein before much manipulation can detach particles of growth along it.

2. Removal of maximal length of renal vein.

'Bloc' Dissection.—The glands, easily commanded by the transdiaphragmatic approach, in several instances looked somewhat ominous. The necessity for routine ablation was proven by positive histology in one case.

The Ureter.—I have met with no evidence of spread down the urinary tract, nor does the literature refer to metastases from parenchymal tumours, although a verbal report of such recently reached me. Suffice it, therefore, to remove what length of ureter is accessible at the nephrectomy site. In the neoplasms growing on the calico-pelvic epithelium, seeding downwards is a well-known complication, and deliberate total ureterectomy is due with the nephrectomy or after a suitable interval as in A. B. (1949). (*Fig.* 306 C.)

NEPHROCOLECTOMY

This may imply partial colectomy anywhere in the large bowel, but for practical purposes it usually means the left colon. It may be called for because a nephroma (or infective lesion) has spread to the overlying colon, or manipulations during a formidable nephrectomy may have damaged colonic circulation. The left colon is renowned for its vulnerable blood-supply.

It proved a feasible and beneficial extension of radical nephrectomy in 2 of my cases. In A. G. H. (1949) the sarcoma had spread to bowel (*Fig.* 302). Resection was followed by immediate re-union and a temporary cæcostomy guarded against tension at the anastomosis. Normal defæcation returned a fortnight later and he left hospital in another ten days. In the case of S. L. W. (pre-1949) the colectomy was done for questionable viability of bowel as a result of the severe measures required in removing the advanced renal growth, and a temporary colostomy seemed best. The continuity was restored two months' later and the bowel was acting normally to the death eleven months later.

Herbert Sugar (1930) reports a case of concurrent nephrocolectomy in a man of 40 years. He restored continuity by immediate end-to-end reunion. The patient was well twelve months later. He considers the extended operation was justified despite the extent of the disease. Aoyama (1925) had a good result in an extensive operation, including colectomy, where inflammatory disease had welded kidney and bowel.

RADIOTHERAPY

Though this is an unpopular weapon in combating primary tumour, Dr. S. Curwen, our radiotherapist, warmly attests to the value of deep X-ray therapy in relieving painful bony metastases of renal carcinomas. He considers that cases suspected of venous spread should be attacked vigorously, as in R. J. H., his general condition being good after the nephrectomy on Nov. 25, 1949. He had deep X-ray therapy, a total dose of 2072 r over 36 days. On March 6, 1950, I found a reddish ovoid swelling about 2 in. in diameter on his scar—a recurrence. Moreover, although it was three weeks since the radiation, he looked sallow and his blood-urea had risen.

In A. G. H. (1949) early recurrence of his fibrosarcoma received deep X-ray therapy. Pain was notably eased, but, tumour and cachexia proceeding apace, he died in March, 1950. In the pre-1949 series, E. I., male, 35 years (my only patient under 40 years), was rejected for operation on his left renomegaly. Adenocarcinoma was found on biopsy and deep X rays were used. Records state: Nov. 13, 1942, tumour dose 4320 r given; Jan. 29, 1943, left loin now empty but recurrence right loin. No further note save death June 27, 1943.

The opposite kidney is liable to serious damage from diffusion of radiation. Hagnar and Coleman's (1934) patient had nephrectomy on July 12, following the completion of preparatory irradiation. Ten days later uræmia started and proved fatal in August. Munger (1937) admits the very marked effect, if in the remaining kidney *nephritis pre-existed,* but asserts that upon the acquired single *normal* kidney the effect disappears upon cessation of the treatment. Portman (1934) subdivides the parenchymal tumours, and, while supporting surgery in the

suprareno-cortical, thinks radiotherapy better in the type arising from tubular and glandular epithelium.

In the embryoma of infancy the effect of radiotherapy is as dramatic as it is disappointing in adult nephroma.

CONCLUSIONS

A series of 10 nephrectomies in 1949 for proven nephromas has been reported with one fatality. A pre-1949 collection of cases is given briefly to amplify discussion data and shed light on prognosis. It includes 2 cases alive and well sixteen and eleven years after operation ; a third died after fifteen years, with a mass of uncertain nature in the liver region. The doctor may expect a 20 per cent 10-year cure rate in the common type, adenocarcinoma.

A revised nomenclature is advocated with *nephroma* as a general clinical title, distinguishing parenchymal cancer as *adenocarcinoma* and the rarer cancer of the lining as *calico-pelvic* epithelioma.

Leading symptoms have been grouped and discussed around the author's experience. The dire need of *hæmaturia* being taken in earnest and treated *as an emergency* by the clinician is stressed. By this means surgery might raise the 10-year cure rate of adenocarcinoma to nearer 40 per cent. The fatal sequel in epitheliomas of the lining is deplored and the role of surgery in preventing this type is signalized.

The merits of the transphrenic approach by Fey's incision are stressed.

The *lethal nature of the venous effluent* of the kidney is demonstrated and, *per contra*, its amenability to surgical control is emphasized.

Nephrocolectomy and radiotherapy are each discussed and illustrative cases quoted.

I wish cordially to acknowledge the patient and enthusiastic help of many registrars, a host of house surgeons, nursing and secretarial staff, which alone made this task possible.

To the editors and publishers of the *Proceedings of the Royal Society of Medicine* and *Bristol Medico-Chirurgical Journal* I am indebted for permission to reproduce *Figs.* 312 (M.A.F.) and 310 (N.W.M.).

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EXPERIMENTAL SURGERY

REGENERATION OF THE CERVICAL SYMPATHETIC

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INTRODUCTION

AN investigation of the conditions which govern the resumption of functional activity of the sympathetic nervous system is desirable at the present time for several reasons. Recent investigations have shown that the apparently simple idea of the progress of recovery along a nerve at a given rate is inadequate, because return of function does not go hand in hand with the simple process of out-growth of new fibres. Such simple concepts are sufficient to deal with the growing tips of the new fibres, where rate of advance can be measured in millimetres per day. But before functional return the new fibres must have matured by increase of diameter and acquisition of a myelin sheath (Young, 1942 ; Gutmann and others, 1942). This process of maturation does not necessarily travel over the axon at the same rate as the tips have advanced. Indeed, it is not certain that it progresses distally at all, for it is now known that the stimulus controlling the maturation comes from the peripheral end of the nerve, from contact with the end-organ (Weiss and Taylor, 1944 ; Sanders and Young, 1944 ; Aitken, Sharman, and Young, 1947).

In order to reach an understanding of the part played by these separate variables it is desirable to study the regeneration in various types of nerve, including those with small medullated and non-medullated fibres. A special reason for such a study is that clinical and experimental studies of sympathectomies have provided results that suggest very high power of regeneration in the sympathetic system (Lee, 1928 ; Simmons and Sheehan, 1939 ; Smithwick, 1940 ; Haxton, 1947 ; Barcroft and Hamilton, 1948). The present investigation is an attempt to provide direct experimental evidence about the rate of regeneration of preganglionic fibres by interrupting the cervical sympathetic trunk and noting the time of return of the function of the eye structures involved and the correlated histological changes in the nerve. Previous experimental studies of regeneration in the sympathetic (Langley, 1900 ;

Lee, 1928; Tower and Richter, 1931 and 1932; Lawrentjew, 1934; Hollinshead and Finkelstein, 1937; Hinsey, Phillips, and Hare, 1939) do not include lesions made at varying levels, which are essential for the proper study of rates of regeneration.

Rabbits and cats were used in this investigation and provided results that differ widely and will be treated separately. Experiments have been confined to the cervical sympathetic.

LESIONS OF THE CERVICAL SYMPATHETIC IN RABBITS

METHOD

Healthy adult rabbits of both sexes were used. It was found that English or Albino rabbits were most suitable as they are phlegmatic and the pupils show up clearly. The fronts of the rabbits' necks were shaved. They were pre-medicated with atropine $\frac{1}{100}$ gr. subcutaneously, given half an hour before operation. They were anæsthetized with intravenous nembutal, 1 gr. per 5 lb. body-weight, and maintained under the anæsthetic with open ether. The operations were conducted with aseptic precautions. A mid-line incision on the front of the neck was made. The carotid sheath was displayed and the cervical sympathetic trunk found, and in every case was confirmed by tracing cranially to the superior cervical ganglion. The lesions made were standardized as follows:—

a. The cervical sympathetic trunk was crushed for ten seconds with fine-pointed watchmaker's forceps. Forceps producing a crush 1 and 2 mm. wide were used. It was found that there was no appreciable difference in the results following these two types of crush (*Table I*). Crushes were placed at varying distances caudal to the superior cervical ganglion.

Table I.—CRUSH IN RABBITS

Distance from ganglion in mm.	A 7	A 7	A 8	A 9	A 16	A 21	B 30	B 33	A 38	B 40	B 42	B 42	B 45	B 51	B 51	B 52	A 52
Days to recover	27	33	34	36	35	39	48	51	51	45	57	60	61	50	56	59	41

A, Crush 1 mm. wide. B, Crush 2 mm. wide.

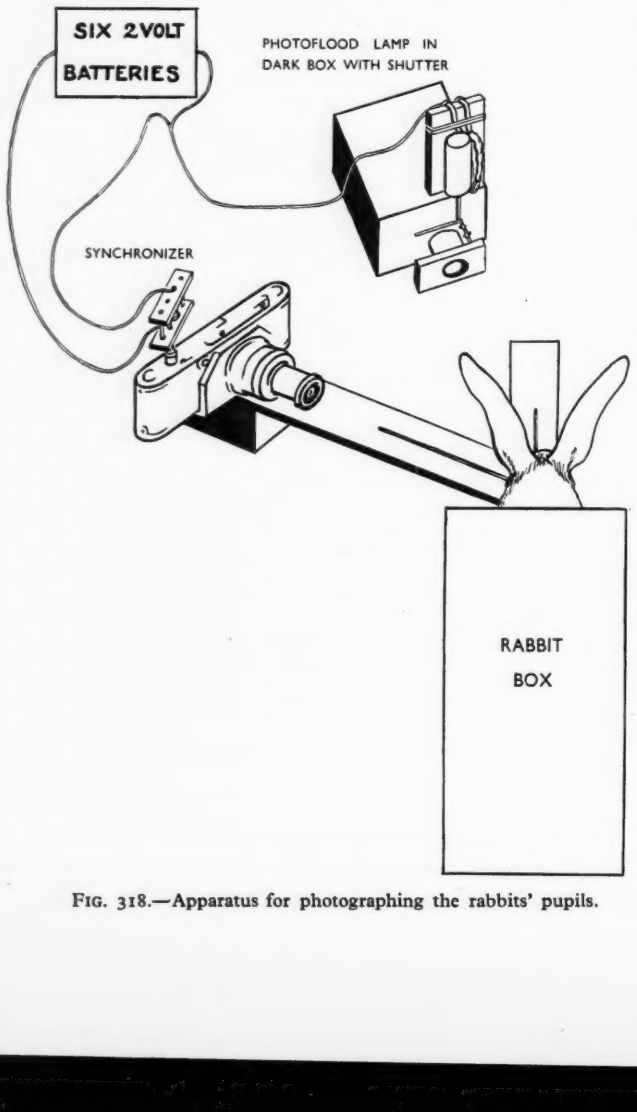


FIG. 318.—Apparatus for photographing the rabbits' pupils.

b. The cervical sympathetic trunk was cleanly sectioned with sharp fine-pointed scissors and the nerve was then mobilized and sutured with human fibrin clot (i.e., a small quantity of human thrombin was added to some human fibrinogen, and 1 drop of this mixture was immediately put on to the cut ends of the nerve which had been placed in apposition). Perfect apposition of the cut ends was not always obtained; sometimes there was retraction of about 1 mm. in the clot.

c. The cervical sympathetic trunk was cleanly sectioned in two places and the intervening portion of nerve removed, leaving a gap. In some cases the lower cut end was placed dorsal to the scalenus anterior muscle.

d. The postganglionic fibres from the superior cervical ganglion were cleanly cut with sharp fine-pointed scissors. The postganglionic fibres usually retracted leaving a gap of about 2 mm.

e. The superior cervical ganglion was cleanly excised, leaving a gap of about 1 cm.

The wound was sewn up in layers with interrupted black silk sutures. Wound suppuration was rare.

The animals were observed at frequent intervals following the operation. The following points were noted:—

1. *The Pupil Size.*—This was the sign chiefly used in estimating the function of the cervical sympathetic. In comparing the pupil size several viewings of each pupil were made, thereby eliminating any pupil changes which might occur as a result of disturbing the animal. Direct visual comparison was found to be the most convenient and reliable method available. The rabbits' pupils were also accurately measured by photographing them under standard lighting conditions with a flashlight synchronized to a 35-mm. camera shutter (*Fig.* 318.) The flash was delivered simultaneously with the camera shutter movement, a speed of $\frac{1}{30}$th second being used. Changes in the size of the rabbit's

pupil are relatively slow, taking place over a period of one or two seconds, so that error from pupil change during the flash was considered negligible. The flash was given by a photo-flood lamp in a light-tight box with a shutter that opened on completion of an electrical circuit by the opening of the camera shutter. This apparatus was kindly lent by Dr. L. C. Thomson. The negatives were of a standard magnification relative to the rabbit's pupil, the same lens and extension tube always being used. 10 seconds for pupillary accommodation was found adequate for comparative purposes. It was also found that the pupils of Albino rabbits photograph most clearly, and those of English rabbits next best. In addition, both these breeds of rabbit are usually not disturbed by being put in a rabbit box to be photographed. Struggling of the rabbit in the box invariably resulted in an increase in pupil size. Photographs were, therefore, taken when the rabbits were tranquil. Photographs measured were only

Table II.—Rabbit No. 1305. April 11, 1949. Left Cervical Sympathetic Trunk crushed 21 mm. caudal to Superior Cervical Ganglion

Date	Day	Observations on Pupils	Left Pupil Measurement	Right Pupil Measurement	Lids	Ears
			Mm.	Mm.		
23.4.49	12	Left pupil smaller	3·8 × 3·2	4·5 × 4·0	Ptosis of left lid	Left ear warmer
3.5.49	22	Left pupil smaller	4·2 × 3·9	5·3 × 4·9	Ptosis of left lid	Left ear warmer
6.5.49	25	Left pupil smaller	4·0 × 3·5	4·7 × 4·0	Ptosis of left lid	Left ear warmer
10.5.49	29	Left pupil slightly smaller	4·1 × 3·8	4·7 × 4·0	Ptosis of left lid	Left ear warmer
12.5.49	31	Left pupil slightly smaller	—	—	No ptosis	Left ear warmer
13.5.49	32	Left pupil slightly smaller	—	—	No ptosis	Ears equal
16.5.49	35	Left pupil slightly smaller	—	—	No ptosis	Left ear warmer
17.5.49	36	Left pupil slightly smaller	—	—	No ptosis	Left ear warmer
18.5.49	37	Left pupil slightly smaller	—	—	No ptosis	Ears equal
19.5.49	38	Left pupil slightly smaller	4·3 × 3·9	5·0 × 4·6	No ptosis	Ears equal
20.5.49	39	Pupils equal	—	—	No ptosis	Left ear warmer
21.5.49	40	Pupils equal	4·2 × 3·9	4·4 × 3·7	No ptosis	Left ear slightly warmer
23.5.49	42	Pupils equal	—	—	No ptosis	Ears equal
24.5.49	43	Pupils equal	—	—	No ptosis	Left ear warmer
25.5.49	44	Pupils equal	—	—	No ptosis	Ears equal
26.5.49	45	Pupils equal	4·5 × 4·4	4·9 × 4·3	No ptosis	Left ear warmer
27.5.49	46	Pupils equal	—	—	No ptosis	Ears equal
28.5.49	47	Pupils equal	—	—	No ptosis	Ears equal
2.6.49	52	Pupils equal	4·1 × 3·8	4·1 × 3·5	No ptosis	Ears equal

The negatives were enlarged and the pupil size measured with dividers against a millimetre scale that was projected in the enlarger simultaneously with the negatives. The rabbit's pupil is unfortunately not circular but of an irregular shape, and following lesions of the cervical sympathetic the distortion of the pupil is increased, and an angulation appears at the lower part, a phenomenon first commented on by Tuckett (1895). The greatest diameter of the pupil was first measured, and then the widest diameter at right angles to this.

Before photographing, the rabbit was kept under standard lighting conditions while pupillary accommodation took place. Initially, maximum accommodation dilatation of the pupil was considered desirable for the photographic records, so the pupils were photographed with a flash after a period in the dark. Trial measurements showed that no appreciable increase in pupil size occurred after 30 seconds in the dark. Later it was decided that a preliminary accommodation to a dim light (25 watts behind the rabbit) was more convenient, and a period of only those in which the pupil was in focus and was approximately perpendicular to the axis of the camera lens.

In order to assess the error in measuring the pupil by this method the following measurements were made :—

a. Photographs of the same pupil taken over a period of an hour under the same conditions showed a variation in measurement of 3·3 per cent. This gives an indication of the accuracy of the technique.

b. Photographs of both pupils of a normal rabbit taken at the same time, when compared, showed a variation of 10 per cent. This gives an indication of the amount of variation in size between the two pupils at any one period.

Table II illustrates the large variation that the normal pupil may undergo from day to day.

2. *The Degree of Ptosis.*—This was found to be less reliable than the pupil size in judging the function of the cervical sympathetic trunk.

3. *The Ear Temperature.*—The temperature of the rabbits' ears was usually compared with that of

the intact side several times by hand at each observation. At one stage in the investigation the temperature of the shaved ears was accurately compared with the aid of a thermocouple sensitive to 0·1° C. It was found that the temperature of the rabbits' ears varied under standard conditions to an extraordinary degree. Readings at half-minute intervals would give very variable results. Proximity of the thermocouple to a small vein would increase the temperature reading of that ear by as much as 2·0° C. These variations are not surprising in view of Grant's (1935) observations of the remarkably rapid changes in calibre of the rabbit's ear vessels, occurring spontaneously and as a result of slight stimuli. The conclusion was finally reached that several alternate manual comparisons of both ear temperatures was the best method of finding out which of the ears was the warmer.

The nictitating membrane was found not to be affected in the rabbit by lesions of the cervical sympathetic.

The animals were usually sacrificed immediately functional return was unequivocal.

They were anæsthetized with nembutal, 1 gr. per 5 lb. body-weight, intravenously, and maintained under anæsthesia with ether. No atropine was given. The cervical sympathetic trunks were dissected out and traced cranially to the superior cervical ganglion. The site of the lesion was identified and measured accurately in mm. caudal to the inferior pole of the superior cervical ganglion. The cervical sympathetic trunk was stimulated caudal to the lesion. Silver electrodes were used. Initially a coil stimulator giving a tetanizing stimulus from a 2-volt battery was employed. Subsequently a Ritchie-Sneath square-wave, multi-vibrator type stimulator giving a well-controlled stimulus was used. Pulses of 0·1 milliseconds and delivered at about 40 cycles per second were used. Under these conditions the normal threshold of pupillary dilatation to stimulation of the cervical sympathetic trunk was found to average 4·5 volts for the rabbit. After each positive reaction to electrical stimulation the cervical sympathetic trunk was crushed just caudal to the superior cervical ganglion and the same stimulus repeated to ensure that the response was not due to stimulation at a distance from the electrodes, or liberation of sympathin at sympathetic nerve-endings caudal to the electrode.

The nerves under investigation were removed from the living rabbit. If possible the nerve was removed both caudal and cranial to the lesion and from the normal side at the same level. Each portion of nerve removed was divided into two and lightly stretched across a small gap cut in a piece of card. Half of the specimens were fixed in Flemming's fixative and stained by Weigert's method, and the other half were fixed either in Bouin's or Bodian's fixative, and stained by Bodian's method for axons. The nerves were embedded in paraffin wax and transverse sections 5μ thick cut.

After microscopical examination, suitable sections were enlarged × 750 and projected on to photographic bromide paper. The medullated fibres or axons, according to the stain used, were then counted. Each fibre was pin-pricked on being counted. In some large nerves, where many fibres were present, a sample count was made as follows: The nerve photograph was divided up into squares 25 mm. × 25 mm. The fibres in about 20 per cent of the squares evenly spaced apart were counted, the fibres touching two sides of each square being included in the count, but not those touching the other two sides. The area of the whole nerve was measured with a planimeter and from this an estimate of the number of fibres in the whole nerve was calculated.

RESULTS

1. Nerve Crush immediately Caudal to the Superior Cervical Ganglion (*Fig.* 319).—Although

FIG. 319.—Nerve crush immediately caudal to the superior cervical ganglion.

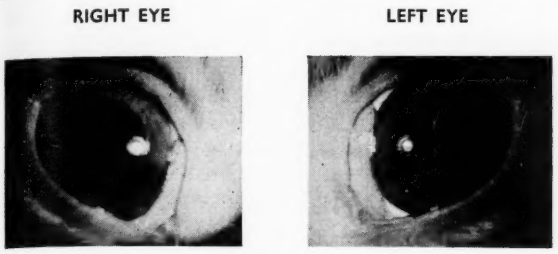
the crush in these cases was made macroscopically caudal to the ganglion, microscopically it was found that ganglion cells extended for some way caudally in the cervical sympathetic trunk beyond the apparent limit of the gangliform swelling.

Following interruption of the cervical sympathetic trunk the pupil on the operated side becomes smaller than the normal pupil (*Figs.* 320–327) and remains so until return of function. *Table II* shows a typical series of observations from which recovery is judged to be on the 39th day. *Table II* also shows the pupil measurements by the photographic method over the same period. A comparison of the pupil measurements of both eyes on the 38th and 40th days also indicates that there is a marked change in the relative pupil size occurring between these two dates. In spite of all attempts to standardize the procedure for viewing and photographing the pupils under standard conditions, the variability remained too great for it to be possible to judge the day on which function returns by a study of one eye alone. The pupil is an index not only of the extent of illumination, but also of the general condition of 'excitement' of the animal.

An attempt was made to evaluate the part played by adrenaline on the pupil after lesions involving the sympathetic supply to the pupil. In two rabbits with lesions of the cervical sympathetic trunk, unilateral adrenalectomy was performed with denervation of the adrenal gland of the opposite side by resection of 1 cm. of the splanchnic nerves and division of branches from the lumbar sympathetic chain to the adrenals. This technique of denervation was checked by staining a denervated gland by Bielschowsky's method for axons, along with a control normal gland. The gland, denervated six days previously, showed no axons.

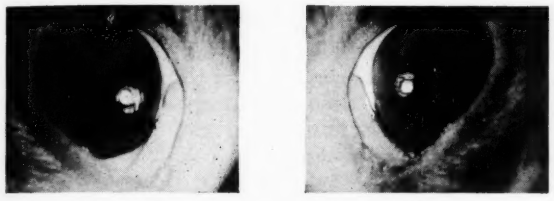
In spite of this procedure, excitement of these rabbits, e.g., banging on the rabbit box while the eyes were being photographed, frequently caused marked pupillary dilatation even on the side of the lesion of the cervical sympathetic (*Figs.* 328–331). Such an effect is presumably due to the liberation of sympathin or nor-adrenaline from sources other

than the adrenals. This finding is in keeping with the observations by Grant (1935) on the adrenalectomized rabbit's denervated ear vessels, and by Stewart and Rogoff (1916) on the cat's denervated



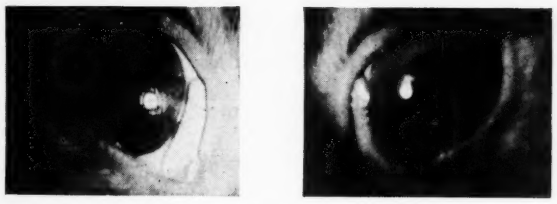
5·3 × 4·9 4·2 × 3·9

Figs. 320, 321.—May 3, 1949, on inspection left pupil appeared smaller.



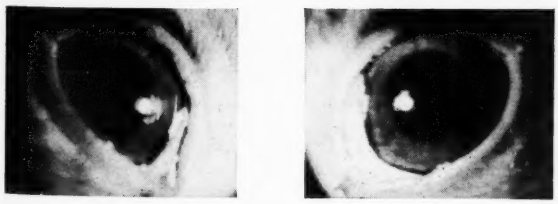
5·0 × 4·6 4·3 × 3·9

Figs. 322, 323.—May 19, on inspection left pupil appeared slightly smaller.



4·4 × 3·7 4·2 × 3·9

Figs. 324, 325.—May 21, on inspection pupils appeared equal.



4·9 × 4·3 4·5 × 4·4

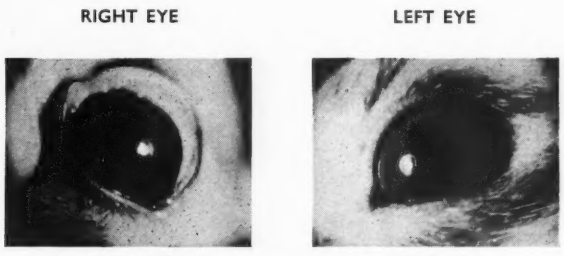
Figs. 326, 327.—May 26, on inspection pupils appeared equal.

FIGS. 320–327.—RABBIT 1305. LEFT CERVICAL SYMPATHETIC TRUNK CRUSHED ON APRIL 11, 1949.

dilator pupillæ after unilateral adrenalectomy and contralateral adrenal denervation. Contradictory evidence is produced by Kellaway (1919) on the effect of asphyxia on the sympathetically denervated pupil of adrenalectomized cats, and by Hartmann and others (1923) on the totally denervated pupil of otherwise similar preparations.

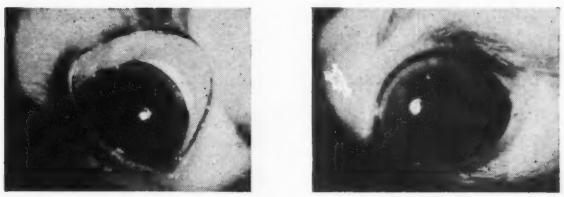
The presence or absence of nervous control was judged by comparing the two pupils. The criterion of unequivocal return of preganglionic function was taken to be equality of the two pupils in cases where the lesion was on one side only. The consistency of the procedure can be judged from 5 rabbits in which the nerve was crushed immediately caudal to the ganglion. Recovery was estimated to have occurred after 30, 32, 34, 34, and 34 days, with a mean of 32·8 days.

In the majority of the experiments the nerves were interrupted on both sides and the criterion of recovery for the side that recovers first is then the becoming *unequal* of the pupils. This criterion might be expected to be more critical than that of



3·2 × 2·8 2·9 × 2·5

Figs. 328, 329.—Control.



3·7 × 3·0 3·5 × 3·1

Figs. 330, 331.—After startling by banging box. N.B.—Dilatation of both pupils

FIGS. 328–331.—RABBIT 1265. LEFT PREGANGLIONIC SECTION. LEFT ADRENALECTOMY, RIGHT ADRENAL DENERVATED.

attaining equality, and also to provide a somewhat earlier estimate, since it does not demand anything approaching complete functional recovery. Actually in 5 animals treated in this way recovery occurred after 19, 28, 29, 31, and 33 days, with a mean of 28·0 days. The animal in which the pupil recovered by 19 days appears to be anomalous, and careful inspection of the notes made from the daily observations on this animal reveals no obvious cause for the disparity. This case has a marked effect in lowering the mean time for regeneration following a crush immediately caudal to the superior cervical ganglion. So far as these short series of experiments go they show that there is no long period of increasing perfection of function after interruption of the nerve by crushing. However, the difference between the means would be expected to occur by chance with a probability greater than 0·05 and less than 0·1 ($t = 1{\cdot}89$, allowing 8 degrees of freedom).

2. Nerve Crush at Varying Distances Caudal to the Superior Cervical Ganglion (*Fig.* 332).—

FIG. 332.—Nerve crush at varying distances caudal to the superior cervical ganglion.

With interruption of the nerve at increasing distances from the ganglion, the times of recovery are increasingly postponed (*Table I* and *Fig.* 333). Care

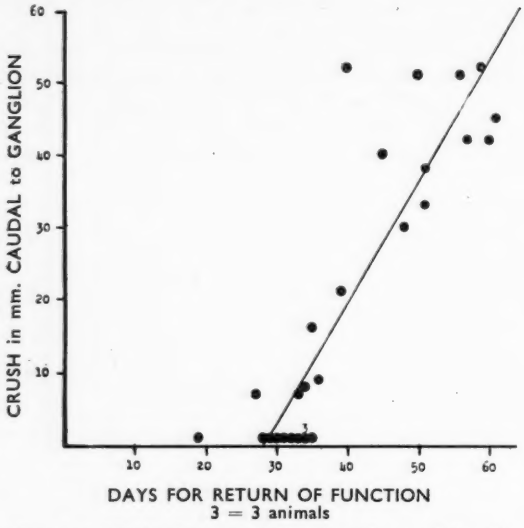


FIG. 333.—Rate of return of function after crushing the cervical sympathetic trunk in rabbits.

is needed in interpreting these results; it must be remembered that they do not represent the rate of advance of the axons tips but a process of maturation to a level sufficient to allow function. The of the regression line. It is interesting to compare this result with the corresponding figure obtained by Gutmann and others (1942) for advance of recovery of motor function following lesions of the rabbit's peroneal nerve. They found recovery advanced 3·05 mm. per day after a latent period of 20·8 days.

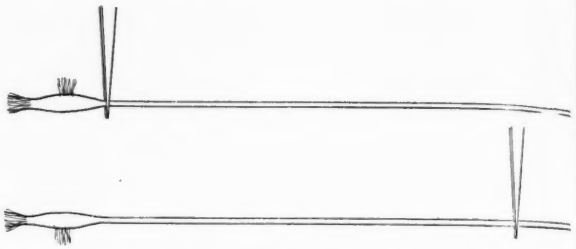


FIG. 334.—Cervical sympathetic trunks crushed high on one side and low on the other.

In 5 of the rabbits the trunk was crushed close to the ganglion on one side and further away on the other (*Fig.* 334), thus providing an estimate of the "advance of functional recovery" for each rabbit (*Table III*). The mean rate calculated in this way (1·9 ± 0·16 mm./day) does not differ widely from that obtained from all the data, but the individual results suggest that the rate is higher when the lesion is nearer to the cell body. A similar result has been found in cats, but it must be remembered that this apparent rate is the resultant of several

Table III.—RATE OF RETURN OF FUNCTION AFTER DELAY PERIOD FOLLOWING PREGANGLIONIC CRUSH IN RABBITS

RABBIT NO.	HIGH CRUSH	LOW CRUSH	DIFFERENCE IN MM.	DAYS HIGH TO REGENERATE	DAYS LOW TO REGENERATE	DIFFERENCE IN DAYS TO REGENERATE	RATE PER DAY
1152	Mm. Immediately below ganglion = 0	Mm. 30	30	28	48	20	Mm. 1·5
1352	8	38	30	34	51	17	1·77
1134	0	42	42	33	57	24	1·75
1137	0	51	51	31	56	25	2·04
1138	0	51	51	29	50	21	2·43

Mean rate = 11·9 ± 0·16 mm./day.

data are not sufficient to describe this increase clearly but it does not depart widely from linearity. Gutmann and others (1942) found a similar situation in the regenerating peroneal nerve of the rabbit studied by a similar method, and fitted straight regression lines to their data. This procedure has been criticized by Sunderland (1947), who has found that over larger distances in man the rate slows down markedly towards the periphery of the nerve. A regression line is simply a means of describing a set of data and reducing them to order, and no one can advocate fitting curved lines in the present circumstances. From the results shown in *Fig.* 333, we may say that the complex of factors influencing regeneration is such that the time of recovery increases with distance from the ganglion in an approximately linear manner and at a rate of 1·56 ± 0·16 millimetres per day, calculated from the slope processes. Before function can return it may be presumed that the following must have taken place: (*a*) The defect in the nerve must have been bridged; (*b*) The new axons must have grown to the ganglion cells; (*c*) The synapses must have been re-established; (*d*) The fibres must have attained a degree of maturity sufficient for full functioning.

From the work of Gutmann and others (1942) it is known that in the rabbit's sciatic nerve following a crush the time taken for (*a*) is 5·2 days, and for (*b*) is 5½ hours per millimetre of nerve. That a similar rate might be found in the sympathetic is indicated by the counting of over 300 axons immediately caudal to the superior cervical ganglion on the 17th day following a crush lesion 19 mm. from the ganglion. In this particular rabbit there was no evidence of return of function or pupil response

on stimulating the nerve, nor would they be expected until about the 40th day (from *Fig.* 333). It must, therefore, be presumed that processes (*c*) and (*d*) are mainly responsible for the lengthy delay, and at present it is purely speculative which of these two takes up the time.

3. Return of Pupil Response to Electrical Stimulation.—It was found that if the preganglionic trunk was stimulated electrically caudal to the crush, immediately following recovery, a pupillary response was almost invariable (*Fig.* 335).

Two rabbits were re-operated six days prior to the calculated date when recovery of pupil diameter

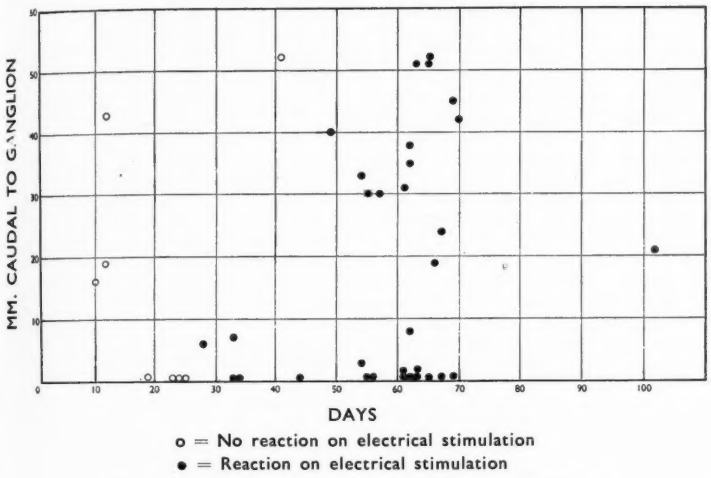


FIG. 335.—Response to electrical stimulation of the cervical sympathetic trunk after crush lesions in rabbits.

was expected. In each case the pupil gave no observable response to electrical stimulation. In each case nine days later the pupil diameter had recovered and stimulation of the cervical sympathetic trunk subsequently confirmed that response to electrical stimulation would then occur. These observations suggest that recovery of pupillary response to electrical stimulation in the cervical sympathetic occurs not long before recovery of pupil diameter.

Table IV.—MEDULLATED FIBRES IN RABBITS' CERVICAL SYMPATHETIC TRUNK

RABBIT NO.	RIGHT	LEFT
1071	1491	764 (Caudal)
1152	651 (Caudal)	945 (Caudal)
1185	684 (Caudal)	1142
1186	712 (Caudal)	994
1203	480	468 (Caudal)
1303	537	394 (Caudal)
1305	1235	1186 (Caudal)
1340	1178 (Caudal)	784 (Caudal)
1352	950 (Caudal)	1714 (Caudal)
1382	800	1062
1412	614	747 (Caudal)

Caudal = Caudal to a lesion.

In 3 rabbits direct electrical stimulation of the cervical sympathetic caused a pupillary reaction before the signs of sympathetic paralysis had completely cleared up, i.e., some ptosis remained or the pupil on the affected side was slightly smaller than normal.

4. Histological Study of Regeneration after Crushing.—

a. Number of Fibres in Normal Rabbits' Sympathetic.—Counts were made of the number of medullated fibres at the mid-cervical region of 14 rabbits' normal sympathetic chains, giving a mean of 819·2 ± 104·8 fibres. Eighteen counts were also made of the nerve caudal to a lesion; it is improbable that this latter count would be greatly different from the normal and this was found to be the case, the mean being 894·7 ± 33·7. The mean for both sets of data is 861·7 ± 49·1. A considerable variation was noticed between two sides of the same animal (*Table IV*).

Counts were made of the number of axons in the mid-cervical region of the rabbits' normal sympathetic seen after Bodian's stain. The mean of the various counts both on normal nerves and nerves central to a lesion was 2091 ± 271·8 (*Table V*). This count will also be affected by the level of the section counted; if a preganglionic fibre synapses half way along the nerve, over 10 × the number of postganglionic fibres are likely to replace the one preganglionic fibre (Billingsley and Ranson, 1918; and Wolf, 1941). A number of isolated ganglion cells were found throughout the length of the cervical sympathetic trunk, and so one would expect the number of medullated fibres to fall off as one went cranially. This might explain the difference in the number of medullated fibres recorded from the two sides of the same animal.

Table V.—AXONS IN RABBITS' CERVICAL SYMPATHETIC TRUNK

RABBIT NO.	NORMAL	CAUDAL TO LESION
1192		1341
1265	3105	2220
1232	1035	
1313		2451
1315		1924
1340		2562

Foley and Dubois (1940) and Foley (1945) have shown that the cervical sympathetic in cats contains a variable percentage of non-medullated fibres. Some of these are non-medullated preganglionic fibres, some are ascending postganglionic fibres, and others descending postganglionic fibres with cells of origin in the superior cervical ganglion.

In order to find out if descending postganglionic axons vitiate the results of axon counts cranial to the lesion in the rabbit's cervical sympathetic after return of function, a 1-cm. segment of the sympathetic trunk was resected in 2 rabbits from the mid-cervical region on both sides. Nineteen days were allowed for degeneration to occur and myelin debris to disappear, and the cranial and caudal portions of sympathetic degenerate as a result of the lesion. For the sake of accuracy of recording, however, the two are distinguished in *Tables IV* and *V*.

The cardiac depressor branch of the vagus joins the cervical sympathetic trunk in the cranial third of its course. It was usually avoided at crushing and at biopsy, but in those cases where it was included with the sympathetic trunk, it was readily

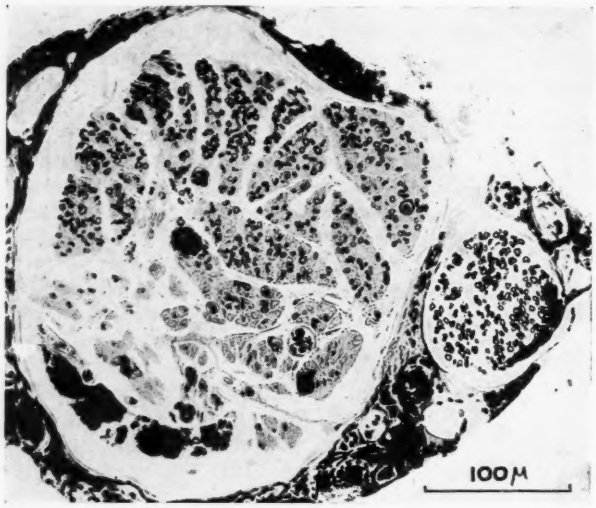


FIG. 336.—Rabbit 1152. Weigert stain. Transverse section. Left (normal side). 945 medullated fibres.

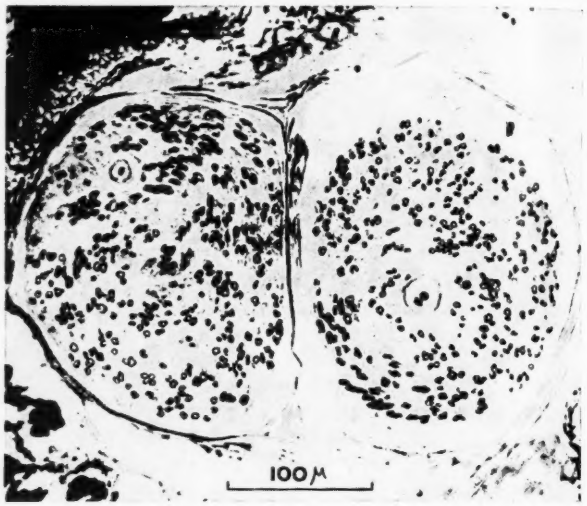


FIG. 337.—Rabbit 1152. Weigert stain. Transverse section. Right, portion of nerve caudal to crush when function has just returned. 651 medullated fibres.

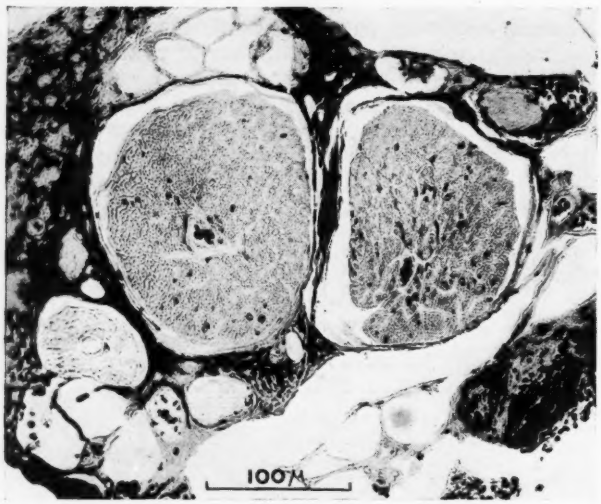


FIG. 338.—Rabbit 1152. Weigert stain. Transverse section. Right, portion of nerve cranial to crush when function has just returned. 44 medullated fibres.

the nerves were removed and stained for both medullated fibres and axons. The cranial portions had neither medullated nor non-medullated fibres, while the caudal portions stained well and appeared to be sections of normal cervical sympathetic. Therefore the non-medullated fibres in the cervical sympathetic trunk of the rabbit are probably all ascending fibres, being either preganglionic or postganglionic fibres.

It is therefore assumed that no fibres visible by Bodian's stain caudal to a lesion of the cervical identified on microscopic examination by its fibre content, as it contains many medullated fibres of larger calibre than are found in the sympathetic.

b. Number of Medullated Fibres Cranial to Lesion when Function Returns.—It was found that the number of definitely medullated fibres in the portion of the cervical sympathetic trunk cranial to the crush when function had just become perfect again was very small. It ranged from 0 to 40 medullated fibres or 0 per cent to 4·5 per cent of the normal number of medullated fibres (*Figs.* 336–338 and *Table VI*).

This phenomenon is striking, especially when considered in relation to the corresponding finding for the rabbit's somatic nerve. Gutmann and Sanders (1943), working on a mixed peripheral nerve, the rabbit's peroneal nerve, found that when motor function had just returned, 50 to 60 per cent of the central stump medullated fibres are present in the peripheral stump.

The degree of medullation of regenerating medullated fibres provides some indication of the degree of maturity of the regenerating fibres. It may well be that the slower conducting preganglionic sympathetic nerves are capable of functioning at a less mature stage than the faster conducting somatic nerves. However, as Gutmann and Sanders (1943) pointed out, full recovery of function in somatic nerves takes place at an early stage in the maturation of the medullated fibres; it may be that with the thinner preganglionic medullated fibres an equivalent degree of maturity has been reached when there are 0 to 4 per cent medullated fibres as when there are 50 to 60 per cent medullated fibres in a somatic nerve.

c. Axons Cranial to a Lesion on Return of Function.—A number of axon counts immediately caudal to the superior cervical ganglion were made as soon as function returned. The axons were very fine and were frequently arranged in groups of about a dozen. Due to the thinness of these regenerating axons, the error of counting is probably great. Results ranged from 465 axons to 2200 axons, or roughly 20 per cent to 110 per cent of the number of axons proximal to the lesion (*Figs.* 339 and 340).

Table VI.—Rabbit Medullated Fibre Count in Cervical Sympathetic Trunk after Return of Function

Rabbit No.	Normal Side	Opposite Side Caudal to Lesion	Regenerated Side Caudal to Lesion	Regenerated Side Cranial to Lesion	Per Cent Regenerated to Normal	Day	Functional State
1127	—	—	—	32	(3·7*)	70	Perfect
1128	—	—	—	21	(2·4*)	65	Perfect
1137	1096	—	—	38	3·46	63	Perfect
1139	—	584	—	11	1·94	61	Perfect
1152	—	945	651	16	2·46	55	Perfect
1315	—	—	1041	18	1·7	54	Perfect
1412	—	—	747	16	2·14	28	Perfect
1143	835	—	—	37	4·43	62	Pupils unequal. Reacts to stimulus
1130	—	—	—	0	0	69	Some ptosis. Reacts to stimulus
1138	—	543	—	0	0	65	Some ptosis. Reacts to stimulus

* Taken as a percentage of the normal mean 861·7 medullated fibres.

d. Medullated Fibres in Newborn Rabbit's Cervical Sympathetic Trunk.—In order to attempt to estimate the importance of medullated fibres in the function of the cervical sympathetic, the cervical sympathetic trunks of two newborn rabbits were sectioned and stained by Weigert's and Bodian's methods. Three medullated fibres only were found in one of the nerves examined. The number of non-medullated axons was only a small percentage of the normal adult value.

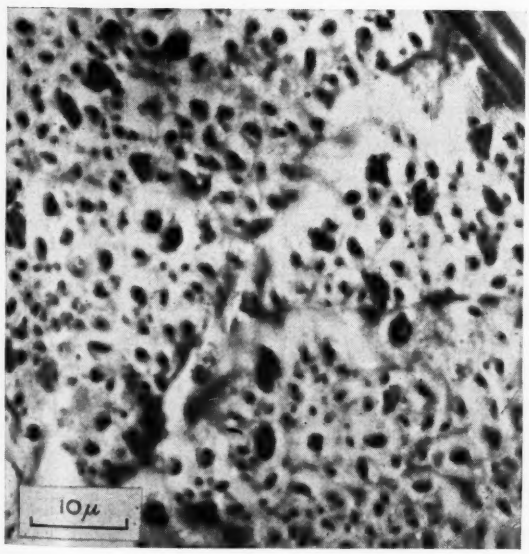


Fig. 339.—Rabbit 1413. Bodian stain. Transverse section. Right, portion of normal nerve.

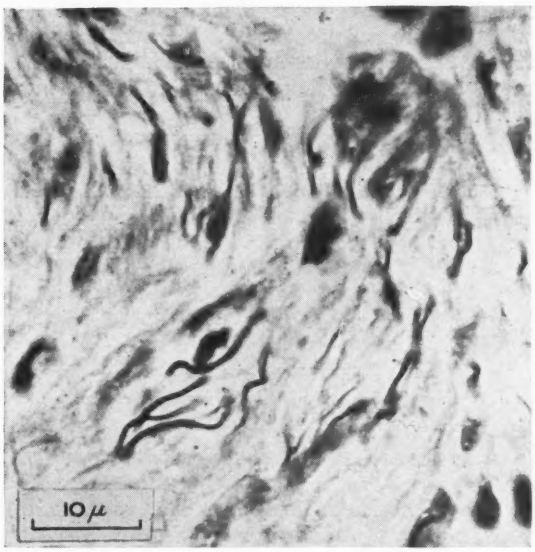


Fig. 340.—Rabbit 1413. Bodian stain. Transverse section. Left, portion of nerve immediately caudal to superior cervical ganglion when function has just returned following a crush. N.B.—Obliquity of the axons.

e. Maturation of Medullated Fibres in the Cervical Sympathetic Trunk.—Nerves removed at increasing intervals following the return of the pupil to normal after crush of the cervical sympathetic trunk, showed a steady increase in the number of medullated fibres. The medullated fibres cranial to a lesion were expressed as a percentage of the fibres caudal to a lesion (*Table VII*).

This result is in conformity with the previously known results of Gutmann and Sanders (1943) on the maturation of medullated fibres in rabbits' peripheral nerves.

Table VII.—Maturation of Medullated Fibres in Rabbits

Rabbit No.	Days since Function Returned after Crush	Medullated Fibre Count Cranial to Lesion
		Per cent
1303	77	47·7
1305	63	23·5
1352, right	29	12·7
1096	26	15·2
1352, left	12	4·9
1327	9 days following section and suture	8·4

5. Section and Fibrin Suture of the Cervical Sympathetic Trunk.—

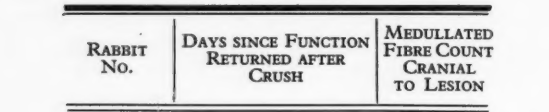


Fig. 341.—Section of the cervical sympathetic trunk on one side.

a. Section on One Side (*Fig.* 341).—In 4 rabbits the cervical sympathetic trunk was sectioned cleanly and sutured with human fibrin clot on one side 1 to 3 cm. from the superior cervical ganglion. After 4 to 5 months there was no evidence of return of function, as judged by pupil size or direct electrical stimulation of the nerve.

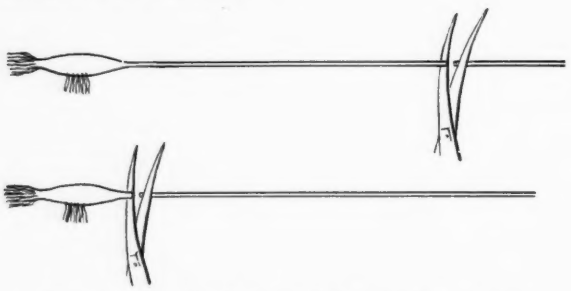


Fig. 342.—Section of the cervical sympathetic trunks, high on one side, low on the other.

b. Section on Both Sides (*Fig.* 342).—In 3 rabbits section and fibrin suture were performed on both sides at varying distances up to 6 cm. from the superior cervical ganglion. In 2 of these rabbits the pupil on one side recovered in 78 and 103 days. At biopsy these pupils responded to electrical stimulation and some fibres were found immediately caudal to the ganglion in the cervical sympathetic trunk on the recovered side.

In 3 of the sutures at biopsy the cut ends were found to be separated by several mm. This was presumably due to movement of the animals' necks after the operation, as no immobilization of the necks was attempted. The remaining 7 sutures were found to be sound at biopsy.

6. Gap in the Cervical Sympathetic Trunk (*Fig.* 343).—In 7 rabbits portions of the cervical sympathetic trunk were resected, leaving gaps up to 30 mm. In no case was there any suggestion of return of function. Six of these rabbits survived till the sixth month, when they were sacrificed. On macroscopic examination of the cervical sympathetic trunk, the caudal end faded away into thin scar tissue. In one case several hundred axons, some medullated, were present in the cranial stump; in one other about 36 medullated fibres were present. In both instances they were evenly distributed throughout the nerve. In view of the absence of functional return, it is possible that these fibres are descending fibres from the superior cervical ganglion (Foley, 1945). This is, however, unlikely in view of the results recorded above in 2 rabbits in which a segment of the cervical sympathetic trunk was resected.

Fig. 343.—Gap in the cervical sympathetic trunk.

7. Section of Postganglionic Fibres (*Fig.* 344).—In 3 rabbits postganglionic fibres immediately cranial to the superior cervical ganglion were sectioned. After section the nerves retracted leaving a gap of about 2 mm. In one rabbit after 101 days the pupil appeared to have returned to normal. However, on stimulation of the cervical sympathetic trunk at 105 and 172 days no reaction of the pupil resulted. In the other 2 rabbits there was no evidence of return of function or reaction to stimulation by 98 and 159 days respectively. In one of these rabbits the scar leading cranially from the ganglion was sectioned and showed axons up to 6 mm. from the ganglion. Anatomical regeneration, therefore, seemed to be progressing, though possible difficulty in finding the peripheral fibres may account for the lack of functional result. However, Tuckett (1895) showed that it took 259 days for functional recovery of the postganglionic fibres from the superior cervical ganglion to occur following crushing in a rabbit, so that it would be very unlikely for recovery of function to occur sooner following section of the postganglionic fibres.

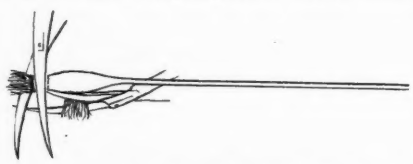


Fig. 344.—Section of postganglionic fibres cranial to superior cervical ganglion.

8. Ganglionectomy (*Fig.* 345).—In 2 rabbits unilateral superior cervical sympathetic ganglionectomy was performed. Over a year later there was

Fig. 345.—Superior cervical ganglionectomy.

no evidence of regeneration functionally, or reaction on electrical stimulation. At the scar numerous axons were seen on microscopic examination.

From general principles it is difficult to imagine that regeneration by the joining of preganglionic to postganglionic fibres can occur without the presence of postganglionic cells. Pye-Smith (1887) found no evidence of regeneration 18 months after excision of the superior cervical ganglion in the rabbit, and this was confirmed by Meltzer (1907), who found no evidence of regeneration 28 months after excision of the superior cervical ganglion in a rabbit. However, such regeneration was claimed by Langendorff (1901) in one cat, and confirmed by electrical stimulation, and by Langley and Anderson (1904), who found that partial functional recovery and response to electrical stimulation occurred in 2 out of 8 cats in under 476 days. The phenomenon was explained by the histological finding of ganglion cells in the pre- or postganglionic fibres in the proximity of the resected ganglion, thus showing that the operation had not been as complete as intended. Foley's (1945) finding of ganglion cells in the cat's cervical sympathetic trunk between the superior and middle cervical ganglia, supports the explanation and findings of Langley and Anderson.

LESIONS OF THE CERVICAL SYMPATHETIC IN CATS

A series of experiments similar to those conducted on rabbits was performed on cats.

METHOD

Healthy adult cats of both sexes were used. No account was taken of minor differences in size and breed.

The cats were anæsthetized with intraperitoneal nembutal and maintained under the anæsthetic with ether. Procedures were similar to those performed on rabbits. In the cat the cervical sympathetic trunk runs with the vagus nerve, bound to the latter by epineurium. It is always smaller than the vagus.

At operation the cervical sympathetic trunk was interrupted at varying levels caudal to the superior cervical ganglion by :—

a. Crushing with fine-pointed watchmaker's forceps giving a crush of 1 mm. for 10 seconds.

b. Simple section of the cervical sympathetic with sharp-pointed scissors. The nerve is prevented from displacement on section by the epineurium binding it to the vagus (the cut ends never retracted more than 0·5 mm.), so no attempt was made to suture the nerve after section.

c. Resection of a portion of the nerve.

In noting the progress of recovery of function, observations at frequent intervals were made of :—

1. *Pupil Size.*
2. *Amount of Ptosis.*
3. *Position of the Nictitating Membrane.*—In the cat, unlike the rabbit, the nictitating membrane is markedly affected by both lesions and stimulation of the cervical sympathetic.
4. *Ear Temperature.*—By manual comparison.

No attempt was made at accurate photographic measurement of the eye changes, or of accurate recording of the ear temperature.

Functional recovery commenced sooner than following similar lesions in the rabbit but was usually not complete in under 4 to 5 days from the first day of returning function. It was found that the order in which recovery took place was characteristic. The ear temperature and nictitating membrane first returned to normal, to be followed later by the recovery of pupil size and ptosis. When the affected eye had apparently returned to normal, it was frequently found that the ear temperature on the recovered side was cooler than that on the control side. These findings are in conformity with those of Machida (1929), who studied postganglionic lesions of the cat's cervical sympathetic trunk. As the period of returning function was prolonged, i.e., 4 to 5 days, the date when the pupil, lids, and nictitating membrane of the affected eye appeared normal was taken as the end-point for the purpose of determining rates of functional recovery.

Table VIII.—Cat. No. C130. JULY 1, 1949. LEFT CERVICAL SYMPATHETIC CRUSHED IMMEDIATELY CAUDAL TO THE SUPERIOR CERVICAL GANGLION. RIGHT TRUNK CRUSHED 13 MM. CAUDAL TO THE GANGLION

DATE AND DAY	PUPILS	LIDS	NICTITATING MEMBRANE	EARS	REMARKS
From 2.7.49 to 9.7.49	Both small, equal	Both ptosed	Both protruded	Equal	
11.7.49, 10th day	Right slightly smaller	Right ptosed	Right protruded	Right ear warmer	
12.7.49, 11th day	Right slightly smaller	Right ptosed	Right protruded slightly	Right ear warmer	
13.7.49, 12th day	Right smaller	Right ptosed	Right protruded slightly	Right ear warmer	No paralytic signs on left side
15.7.49, 14th day	Right slightly smaller	Right ptosed slightly	Right protruded slightly	Right ear warmer	No paralytic signs on left side
16.7.49, 15th day	Right slightly smaller	Right ptosed slightly	Right protruded slightly	Right ear warmer	No paralytic signs on left side
20.7.49, 19th day	Pupils equal	Equal, no ptosis	Equal	Equal	Both eyes appear equal and normal

At biopsy the cats were anæsthetized with intraperitoneal nembutal and maintained under anæsthesia with ether. No atropine was given as it interfered with the pupillary response on stimulation of the cervical sympathetic. The procedure was essentially the same as that for rabbits. The normal threshold for electrical stimulation of the cervical sympathetic trunk to cause a reaction of the dilator pupillæ muscles was found to be 2·25 volts, delivered with a pulse of 0·1 milliseconds at about 40 cycles per second.

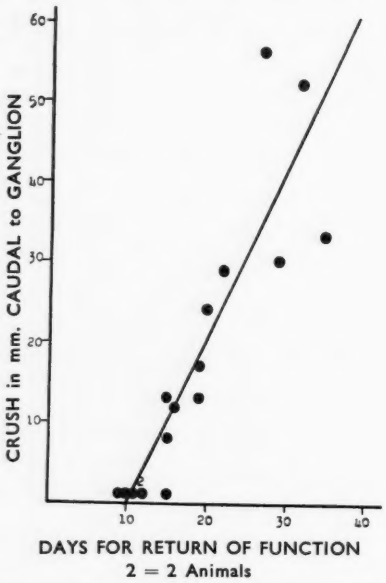


FIG. 346.—Rate of return of function following crush of the cervical sympathetic trunk in cats.

RESULTS

1. Nerve Crush immediately Caudal to the Superior Cervical Ganglion.—*Table VIII* shows a typical series of observations on a cat with a lesion immediately caudal to the superior cervical ganglion on one side and at a distance on the other side. From this, function was judged to have returned at 12 days on the left side and at 19 days on the right side, taking full return to normal of the eye structures as the criterion of recovery.

In 6 cats with a crush immediately caudal to the ganglion, recovery had occurred by 9, 10, 11, 12, 12, and 15 days, with a mean of 11·5 days. In all except one of these animals (which recovered on the 15th day) the nerve on the opposite side had been crushed at a distance from the ganglion.

2. Nerve Crush at Varying Distances Caudal to the Superior Cervical Ganglion.—As with the rabbit it was found that with interruption of the nerve at increasing distances from the ganglion, return of function is progressively delayed (*Table IX*, *Fig.* 346). The results as plotted on a graph suggest a linear relationship between distance from the lesion and time for function to return. The slope of a straight regression line, when fitted, gives a "rate of advance of functional recovery" of 2·03 ± 0·27 mm./day. However, when the "rate of advance of functional recovery" is calculated for 5 of the cats in this series, the rate is seen to increase as the distance from the ganglion increases, which suggests, as in the rabbit, that the rate is faster the nearer the lesion is to the cell-body. The mean of rates calculated in this way is 2·66 ± 0·37 mm./day (*Table X*).

Table IX.—CRUSH IN CATS

Distance from ganglion in mm.	8	12	13	13	17	24	29	30	33	52	56
Days to recover	15	16	15	19	19	20	22	29	35	32	27

3. Return of Ocular Response to Electrical Stimulation.—All the animals responded to electrical stimulation of the cervical sympathetic trunk when recovery of the ocular signs had occurred.

Table X.—RATE OF RETURN OF FUNCTION AFTER DELAY PERIOD FOLLOWING PREGANGLIONIC CRUSH IN CATS

CAT No.	HIGH CRUSH	LOW CRUSH	DIFFERENCE IN MM.	DAYS HIGH TO REGENERATE	DAYS LOW TO REGENERATE	DIFFERENCE IN DAYS TO REGENERATE	RATE PER DAY
C130	Mm. Immediately below ganglion = 0	Mm. 13	13	12	19	7	Mm. 1·86
C131	0	17	17	12	19	7	2·43
C134	0	24	24	9	20	11	2·18
C127	0	34	34	10	22	12	2·83
C116	12	56	44	16	27	11	4·0

Mean rate = 2·66 ± 0·37 mm./day.

4. Histological Study of Regeneration after Crushing.—

a. Number of Fibres in Normal Cats' Sympathetic.—This has been carefully studied in cats by Foley and Dubois (1940) and Foley (1945), who found the number of axons varied between 5121

and 10,563, and the number of medullated fibres ranged from 2373 to 7519; 6 counts of medullated fibres and 3 counts of axons made in this present series fell within these limits.

b. Number of Medullated Fibres Cranial to the Lesion when Function Returns.—As in the rabbits, it was found that the number of medullated fibres distal to the lesion when function had just returned was very small, ranging from 0 to 136, or 0 to 2·7 per cent of the normal number of medullated fibres (*Table XI, Figs.* 347 and 348).

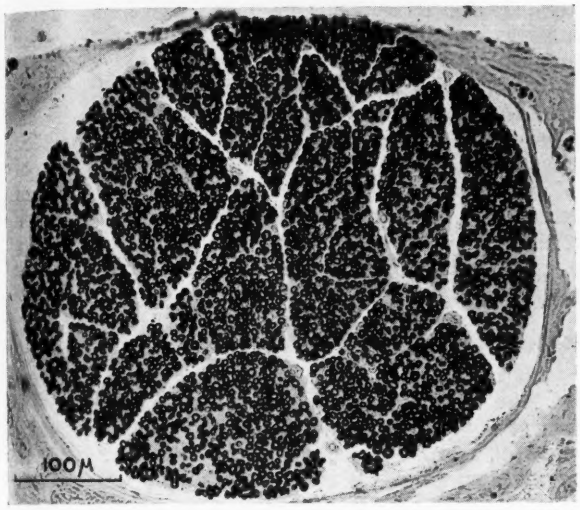


FIG. 347.—Cat 114. Weigert stain. Transverse section. Left, portion of nerve caudal to crush when function has just returned.

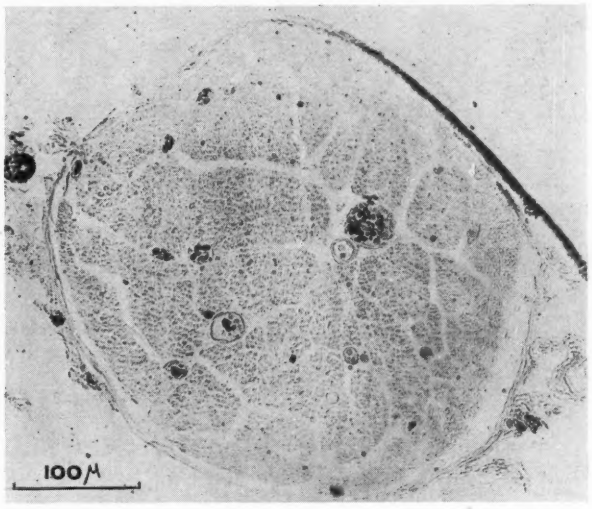


FIG. 348.—Cat 114. Weigert stain. Transverse section. Left, portion of nerve cranial to crush when function has just returned.

c. Number of Axons immediately Caudal to the Superior Cervical Ganglion when Function Returns.—Three counts only were made of this, but they indicate the order of the number. The figures are as follows, the figure in brackets being the number of axons in the same nerve proximal to lesion: 5628 (5369), 3072, 6022.

Table XI.—CAT MEDULLATED FIBRE COUNT IN CERVICAL SYMPATHETIC TRUNK AFTER RETURN OF FUNCTION

CAT NO.	MEDULLATED FIBRES CAUDAL TO LESION	MEDULLATED FIBRES CRANIAL TO LESION	PER-CENTAGE OF NORMAL	FUNCTION
C92	5017	136	2·7	Perfect
C131	5970	About 68	1·1	Perfect
C116	—	About 60	—	Perfect
C134	—	About 40	—	Perfect
C133	—	22	—	Perfect
C130	—	20	—	Perfect
C113	—	8	—	Perfect
C107	4687	0	0	Perfect
C114	3570 (normal side)	0	0	Perfect
C127	—	0	0	Perfect
C121	—	0	0	Some ptosis
C105	(After gap)	19	—	Perfect

d. Descending Fibres in the Cervical Sympathetic Trunk.—In 2 cats a 1·5-cm. segment of the cervical sympathetic was resected from the mid-cervical region on both sides. After 16 days there was no evidence of return of function and the animals were sacrificed. The gaps were not macroscopically bridged. Three of the nerves cranial to the gaps showed no more than several hundred scattered axons and up to six medullated fibres. It is considered that these fibres are descending fibres. In one nerve examined no fibres were found. It may, therefore, be assumed that the vast majority of the axons counted immediately caudal to the superior cervical ganglion in the cat when function has just returned are regenerating ascending fibres.

5. Nerve Section immediately Caudal to the Superior Cervical Ganglion.—In 7 cats with the cervical sympathetic trunk sectioned immediately caudal to the ganglion, recovery had occurred by 7, 11, 12, 12, 12, 13, and 13 days with a mean of 11·4 days. In all of these animals the nerve on the opposite side had been sectioned at varying levels from the ganglion. Care had to be taken not to injure the vagus nerve, which is closely bound to the sympathetic, and thereby allow cross union to occur. In the animal in which recovery had occurred by the 7th day it is highly probable that all the sympathetic fibres to the superior cervical ganglion were not anatomically severed, as the delay before return of function is exceptionally short. Omitting this one animal the mean is 12·2 days.

6. Nerve Section at Varying Distances Caudal to the Superior Cervical Ganglion.—The increase in time for recovery to occur with increasing distance of the lesion from the ganglion was well shown (*Table XII, Fig.* 349). The points on the graph suggest a linear relationship, and a straight regression line, when fitted, gave a "rate of advance of functional recovery" of 1·6 ± 0·1 mm./day. "Rates of

advance of functional recovery" as calculated for individual cats (*Table XIII*) appear to bear no relation to the distance from the ganglion. They give a mean of 1·71 ± 0·07 mm./day.

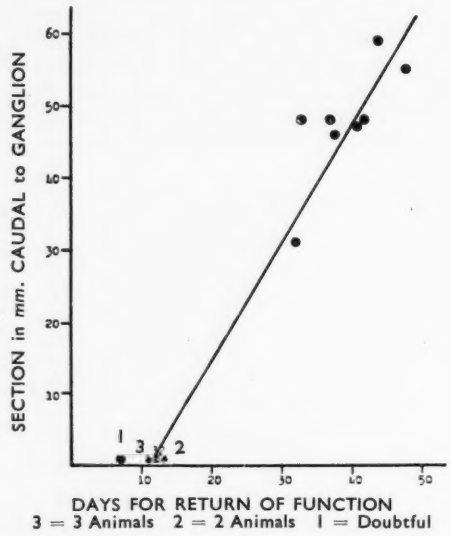


FIG. 349.—Rate of return of function following section of the cervical sympathetic trunk in cats.

On comparing the slopes of the regression lines following crush and section in cats there is no

Table XII.—SECTION IN CATS

Distance from ganglion in mm.	31	46	37	48	48	48	55	59
Days to recover	32	38	41	33	37	42	48	44

significant difference, the probability that such a difference would occur by chance being greater than 0·1 and less than 0·2 ($t = 1{\cdot}55$, $f = 28$).

7. Gaps in the Cervical Sympathetic Trunk.—Data for 2 cats only are available. In one cat, after resection of a 10-mm. portion of the cervical sympathetic trunk, 11 mm. caudal to the ganglion, functional recovery was complete by 47 days. On histological examination numerous axons were seen bridging the gap and at the distal end of the gap 2487 axons were counted, all within the nerve-bundles of the cranial stump. Of these fibres, only 19 were medullated. The number of axons 6 mm. caudal to the end of the caudal stump was 5196 and may be taken to represent the normal number of axons in the nerve, i.e., about 48 per cent of fibres had grown through to the ganglion cells when function had returned (*Figs.* 352–354).

In the other cat 9 mm. of the cervical sympathetic trunk was resected 25 mm. from the superior cervical ganglion, and the central (caudal) stump was placed lateral to the sternomastoid muscle, leaving a gap of 16 mm. between the two cut ends. No signs of return of function had occurred by six months, when at biopsy the caudal stump was found to terminate in a neuroma, the gap between the two cut ends remaining unbridged.

DISCUSSION

On comparing the results of lesions in the cat and the rabbit, a striking species difference is observed. The delay period before function returns following a crush immediately caudal to the superior cervical ganglion is considerably shorter in cats (mean of 11·5 days) than in rabbits (mean of 30·4 days). The "advance of functional recovery" is also faster in cats than in rabbits, as is seen by comparing figures obtained from regression lines of all the animals as plotted on a graph (*Figs.* 333, 346), and also for the rates as calculated for individual animals (*Tables III* and *X*). The difference between the species is even more marked when the results of section of the nerves are compared. In the cat regeneration following simple section without suture appeared to occur almost as readily as following the corresponding crush lesion. These results are consistent with those of Lee (1928), who sectioned the cervical sympathetic trunk at a fixed distance (2 cm.) caudal to the superior cervical sympathetic ganglion. However, in the rabbits studied after section and suture with human fibrin clot, functional recovery was exceptional, even though periods of

Table XIII.—RATE OF RETURN OF FUNCTION AFTER DELAY PERIOD FOLLOWING PREGANGLIONIC SECTION IN CATS

CAT NO.	HIGH SECTION	LOW SECTION	DIFFERENCE IN MM.	DAYS HIGH TO REGENERATE	DAYS LOW TO REGENERATE	DIFFERENCE IN DAYS TO REGENERATE	RATE PER DAY
	Mm.	Mm.					Mm.
C149	0	31	31	12	32	20	1·55
C142	0	46	46	13	38	25	1·84
C144	0	48	48	12	37	25	1·92
C143	0	48	48	13	42	29	1·66
C136	0	59	59	7	44	37	1·60

Mean equals 1·71 ± 0·07 mm./day.

The number of medullated fibres present cranial to the section when function had just returned ranged from 0 to 45 finely medullated fibres. The number of axons present at the same time was similar to those present cranial to a lesion when function had just returned following a crush (*Figs.* 350, 351).

4 to 5 months were allowed for return of function. It is possible that the human fibrin has an inhibitory effect on the regeneration of sympathetic fibres in the rabbit, though this would appear unlikely, as suture of the rabbit's peripheral nerves to the sympathetic with human fibrin clot does not exert an inhibitory influence (Evans, 1947).

From the few experiments on the effect of gaps in the cervical sympathetic in both animals, the same conclusion may be drawn, i.e., that the cat is capable of much greater regenerative power in the sympathetic system than the rabbit. Lee (1928) found that in the cat gaps up to 4 mm. in the cervical sympathetic trunk offered little resistance to regeneration, merely doubling the time for regeneration to occur, compared to the time following section and suture. He records the remarkable instance where the two cut ends were separated by a gap of 25 mm., which was bridged by the fibres regenerating through the interposed sternomastoid muscle in 275 days. This regeneration was evidenced by the return of the pupil to normal, a positive reaction to nerve stimulation caudal to the gap, as well as by histological evidence of regenerated axons.

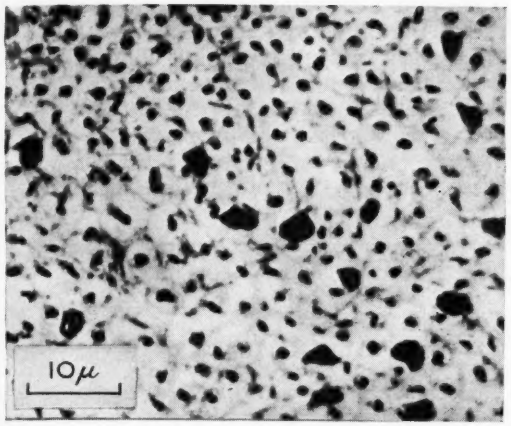


FIG. 350.—Cat 136. Bodian stain. Transverse section. Right, portion of nerve caudal to section when function has just returned.

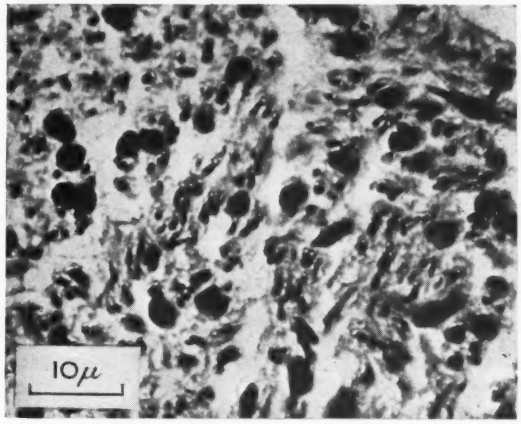


FIG. 351.—Cat 136. Bodian stain. Transverse section. Right, portion of nerve cranial to section when function has just returned.

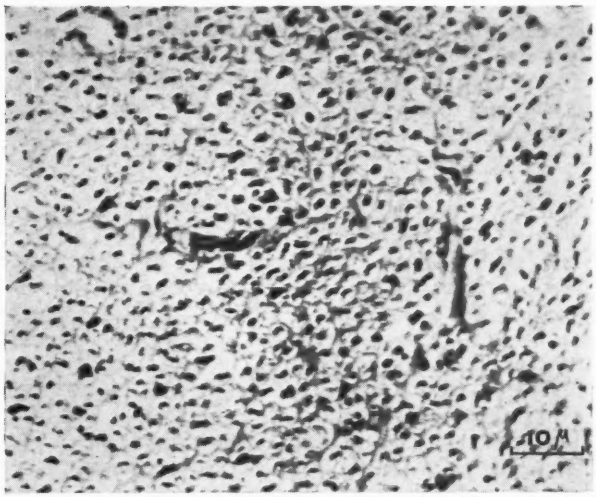


FIG. 352.—Cat 105. Bodian stain. Transverse section. Left, portion of nerve caudal to gap when function has just returned. About 5196 axons.

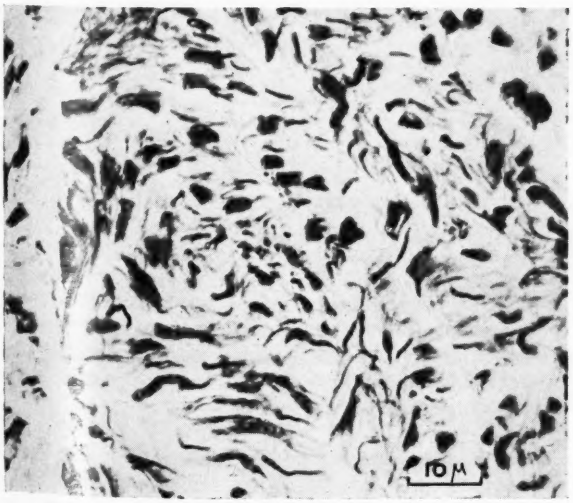


FIG. 353.—Cat 105. Bodian stain. Transverse section. Left, portion of nerve cranial to gap of 1 cm. when function has just returned. About 2487 axons. N.B.—Obliquity of axons and numerous Schwann-cell nuclei.

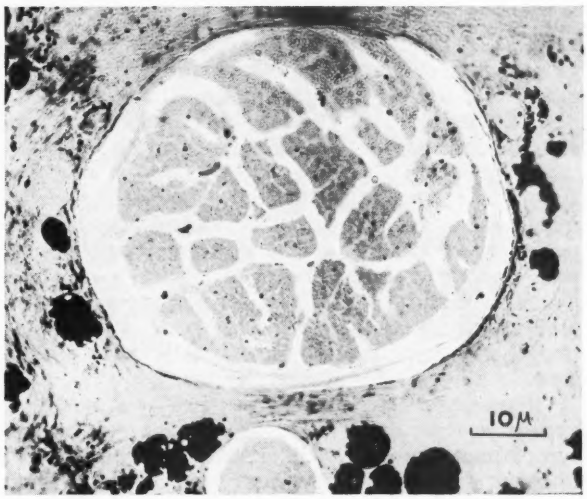


FIG. 354.—Cat 105. Weigert stain. Transverse section. Left, portion of nerve cranial to gap of 1 cm. when function has just returned. 19 medullated fibres.

The results of numerical evaluation of the number of medullated and non-medullated fibres immediately caudal to the superior cervical ganglion when function and response to electrical stimulation has just returned, is remarkably similar in both rabbits and cats, following either crush lesions, sections, or actual gaps. The number of axons counted thus, in both cats and rabbits, ranged from 20–110 per cent of the number in the nerve caudal to the lesion, but only a small percentage of them (0–4·43 per cent) had matured sufficiently to be medullated (*Tables VI* and *XI*). Most of these axons were thinner than normal.

In any study involving examination of the fibres in the cat's cervical sympathetic trunk, the findings of Foley and Dubois (1940), and Foley (1943, 1945), are of considerable importance. These workers, using the pyridine silver technique for staining axons, found a considerable proportion (37·5 per cent) of the fibres in the cat's cervical sympathetic to be non-medullated. The cells of the superior cervical ganglion may project caudally a fascicle of postganglionic sympathetic fibres. This descending sympathetic fascicle usually leaves the cervical sympathetic trunk in the upper portion. Foley (1945) also found several hundred widely scattered descending axons from the superior cervical ganglion in the cervical sympathetic trunk, a finding that is confirmed in 2 cats in the present paper.

As well as the three cervical sympathetic ganglia usually described, it is now known that ganglion cells are distributed throughout the cervical sympathetic trunk (Foley, 1945). Observations on the present series confirm this finding in rabbits as well as cats. These cells send the majority of their postganglionic axons caudally, though they may send several hundred axons cranially. In regeneration experiments, therefore, if ganglion cells are situated between the lesion and the superior cervical ganglion, they will be found in sections of the nerve immediately caudal to the superior cervical ganglion.

Following the work of Billingsley and Ranson (1918) in man, and of Wolf (1941) in cats, it would appear that for each preganglionic fibre in the cervical sympathetic there exist between 11 and 32 ganglion cells and postganglionic fibres. Hence ganglion cells scattered throughout the length of the cervical sympathetic trunk will modify the fibre content considerably at different levels.

In a small percentage of cats (4–10 per cent) Foley (1945) found that the vagus sends a fascicle into the cervical sympathetic which descends in the periphery of the nerve as a discrete group of fibres and does not intermingle with the sympathetic fibres. These vagus fibres are identified by their large calibre. In the series of cats described in this paper, this fascicle from the vagus was occasionally seen.

The ready manner in which preganglionic fibres appear to regenerate following clinical preganglionic sympathectomy is well known (Simmons and Sheehan, 1939; and Smithwick, 1940). It is also possible that only a few functioning preganglionic fibres are necessary for full sympathetic function. The findings of Billingsley and Ranson (1918), and of Wolf (1941), indicate that one preganglionic fibre has an effect on a number of ganglion cells. This theme is further exemplified by the work of Simeon, Cannon, and Rosenblueth (1938), who showed that following partial section of the preganglionic fibres in the cervical sympathetic trunk of cats, stimulation of the remaining intact fibres caused an effect of the same amplitude as stimulating the intact trunk. Fitting in closely with this phenomenon is the work of Brücke (1937), who found that following preganglionic section, the concentration of cholinesterase in the superior cervical ganglion is considerably decreased. Hence a small amount of acetylcholine might have an exceptionally great effect following a preganglionic lesion.

SUMMARY

An experimental study of regeneration of the cervical sympathetic in rabbits and cats is recorded.

1. A marked species difference was noted in comparing the regeneration of the sympathetic in rabbits and cats. In general, the sympathetic of cats regenerates faster and more readily than that of rabbits when subjected to similar lesions.

2. Following a crush, 1 to 2 mm. wide, of the cervical sympathetic trunk in 22 rabbits, after a mean delay of 30·4 days, function returned in an apparently linear manner at a mean rate of 1·56 ± 0·16 mm./day.

3. Following a crush 1 mm. wide of the cervical sympathetic trunk in 11 cats, after a mean delay of 11·5 days, function returned in an apparently linear manner at a mean rate of 2·03 ± 0·27 mm./day.

4. Return of function following section and suture of the cervical sympathetic trunk in rabbits with human fibrin clot is rare within 4 to 5 months.

5. Return of function following simple section of the cervical sympathetic trunk in 8 cats occurred after a mean delay of 11·4 days, at a mean rate of 1·6 ± 0·1 mm./day.

6. Function returned in 47 days following the making of a gap of 1 cm. in the cervical sympathetic trunk in a cat, but not in rabbits.

7. In the cervical sympathetic trunk of the rabbit the normal number of axons is 2091 ± 271·8 and the normal number of medullated fibres is 861·7 ± 49·1.

8. The number of axons immediately caudal to the superior cervical ganglion of the rabbit when function has just returned following a crush is between 465 and 2200 axons, i.e., 20–110 per cent of the number caudal to the lesion. Only 0 to 40 of these are medullated fibres.

9. The number of axons immediately caudal to the cat's superior cervical ganglion when function has just returned following crush lesion, section, or a gap is similar to the rabbit, being approximately 48–105 per cent of the number caudal to the lesion, or between 2487 and 6022 axons, and including only 0 to 136 medullated fibres.

I am much indebted to Professor J. Z. Young for advice and criticism, to Dr. D. A. Sholl for help with the statistics, and to Mr. J. Armstrong, Mr. R. H. Ansell, and Miss R. J. Robbins for technical help.

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SHORT NOTES OF RARE OR OBSCURE CASES

SPONTANEOUS RUPTURE OF AN UMBILICAL HERNIA IN AN INFANT

BY A. BRUCE MACLEAN, GLASGOW

THE condition of umbilical hernia in infancy is met with frequently and seldom gives rise to complications which merit comment. As a rule the advice given to the mother is to strap the abdomen in such a way as to approximate the recti abdominis muscles and allow the physiological process of obliteration of the umbilical cicatrix to proceed. In the majority of infants this is successful, and as complete closure is obtained in three years or so, operative intervention is seldom necessary.

This method is applicable to all sizes of hernia, and despite the apparent thinness of the skin and underlying tissue in some, one has never had any worries as to the management of this type of case, the possibility of rupture never being entertained.

CASE REPORT

A male child of 3 months was admitted to hospital on June 17, 1949. The history was that two hours prior to admission, while the mother was changing the napkin following a severe bout of crying, it was noticed that the umbilicus had given way and small bowel was lying free on the abdominal wall. An umbilical hernia had been present since birth, otherwise the child had thriven and developed normally.

The infant was small and undernourished and in a state of severe shock; it was cyanosed and the pulse was uncountable. The appearances generally were those of a dying infant.

On examination of the abdomen it was noted that about three feet of congested small intestine had prolapsed through a ruptured umbilical hernia.

Operation was undertaken immediately under nitrous oxygen and cyclopropane anæsthesia. The neck of the sac was enlarged and the bowel replaced after cleaning with saline and flavine. The peritoneum was then closed and the aponeurosis repaired. The redundant skin was removed and the wound sutured. The skin removed showed no evidence of inflammation or ulceration.

Following the replacement of the small bowel the condition of the infant improved dramatically, and despite the soiling of the intestine and presumably contamination of the peritoneal cavity, convalescence was uneventful.

COMMENT

That this condition is rare is indeed true. I have been unable to find a similar case in the literature. Hunziker (1946) reports a spontaneous rupture of an umbilical hernia occurring in a female of 69 years during an epileptiform seizure.

In the case reported here a bout of crying must have raised the intra-abdominal pressure sufficiently to rupture the thinned but normal skin covering the sac.

My thanks are due to Mr. Matthew White, in whose wards this case was treated.

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ABDOMINAL ACTINOMYCOSIS FOLLOWING A PERFORATED DUODENAL ULCER

By F. P. RAPER

SURGICAL TUTOR, UNIVERSITY OF LEEDS

ABDOMINAL actinomycosis most commonly arises in relation to the appendix or the ileocæcal region of the bowel, but there are a few published cases in which it followed a perforated peptic ulcer. Keynes (1924), reporting a series of 21 cases of actinomycosis, included 1 case which followed a perforated gastric ulcer. Bates (1933) mentioned 1 case following a perforated duodenal ulcer amongst 29 consecutive cases of actinomycosis at the London Hospital. Cope (1938) quotes a case report from Gordon-Taylor. Shearburn (1943) reports 2 cases of actinomycosis of the stomach and duodenum, the second being one of extensive upper abdominal actinomycosis following a perforated 'peptic' ulcer.

Actinomyces bovis is a frequent inhabitant of the mouth and alimentary canal and there is no reason why a duodenal ulcer should not harbour the organism. However, several cases have been reported of an actinomycotic granuloma in the wall of the stomach or duodenum. Such reports include those by de Courcy Wheeler (1928), Nathan (1929), Behring (1933), Blain (1933), Rabinowitz (1933), Shearburn (1943), and Fuller and Wood (1945). It is not known whether the patient reported here had a primary actinomycotic lesion of the duodenum or whether the actinomycetes were inhabitants of a pre-existing duodenal ulcer.

CASE REPORT

HISTORY.—The patient, a married woman aged 25, was admitted to the General Infirmary at Leeds in March, 1945, with a perforated duodenal ulcer. She was then in the Land Army and her duties consisted largely of a milk-round. For two weeks prior to the perforation she had vague indigestion. There was nothing unusual about the appearance of the perforated ulcer, but there was a considerable amount of slimy, white, opalescent fluid in the abdomen and a small cyst was noted in the right ovary. The perforation was sutured and covered with omentum, the appendix looked normal, and was removed, and the abdomen was closed, leaving a drain into the pelvis through a small suprapubic incision. The immediate post-operative progress was uneventful and she was discharged from hospital on the nineteenth day with the wounds healed.

June, 1945: Re-admitted to hospital for curettage of three abscesses in the scars. These had formed about four weeks after discharge from hospital and kept filling and bursting. Two of the abscesses were small and lay in the paramedian scar; one larger abscess was in the suprapubic wound. All were curetted, but the suprapubic abscess was found to extend into the pelvis and a drain was therefore left in it after curetting the cavity. Culture of the pus from these abscesses grew *Staph. aureus* and *B. coli*. The abscesses did not heal until October.

December, 1945: Re-admitted to hospital with a generalized peritonitis originating from a pelvic abscess. She was very ill and had lost weight markedly. The abdomen was explored and the intestines were found to be so matted together that it was not possible to determine the origin of the pelvic abscess. The pelvis was drained, but on culture the pus was sterile. In January, 1946, whilst still in hospital, she suddenly coughed up 3 oz. of pus and a radiograph of the chest showed inflammatory changes at the left base. She was given 16,000 units of penicillin 3-hourly for eight days. The cough subsided and the drainage from the lower abdomen ceased. She was discharged from hospital in February.

March, 1946: Re-admitted to hospital. All the wounds had healed, but a slightly tender, firm, fixed swelling could be felt in the lower part of the left iliac fossa. It was also palpable on rectal examination. No treatment was ordered and she was kept under observa- as an out-patient.

May, 1946: Re-admitted for incision of the swelling in the left iliac fossa, which had become larger and more tender and was involving the skin. On incision a small quantity of necrotic material escaped, but culture of it was sterile. She was discharged after a few days and during the summer her general condition improved, but the incision in the left iliac fossa never healed.

January, 1947: Re-admitted to hospital for incision of a left ischiorectal abscess. The pus again was sterile, but she was given 16,000 units of penicillin 3-hourly for eight days. The wound in the left iliac fossa continued to drain. Discharged from hospital in February.

April, 1947: A tender swelling was developing in the right ischiorectal fossa, but on treatment with short-wave diathermy it subsided. Her general condition was improving, but sinuses were still present in the left iliac fossa and left ischiorectal fossa.

October, 1947: Re-admitted because of a small abscess in the right lumbar region. This was incised and found to be in the lumbar muscles. Radiographs of her spine and renal tract were normal. Examination of the pus showed that it was sterile, but filaments suggestive of actinomycosis were seen. Attempts to culture the actinomycosis failed. She was then given 10·5 mega-units of penicillin in three weeks and Lugol's iodine (30 min. t.d.s.). When discharged in December, 1947, the sinuses had almost healed.

January, 1948: Re-admitted because of a small abscess in the left lumbar region. The sinus in the left iliac fossa had healed, but in the left ischiorectal fossa and the right lumbar region the sinuses were still open. The left lumbar abscess was incised and a strain of actinomycosis was cultured from the pus and found to be very sensitive to penicillin. (Growth inhibited by a concentration of 1/400 unit/c.c. of penicillin.) She was then given 96 mega-units of penicillin in fifty days in addition to 30 min. of iodine t.d.s. In April, 1948, she was discharged from hospital. All the sinuses had healed and she was gaining weight.

She was seen in October, 1949, when her health was good. She has no indigestion and there is no sign of recurrence of the actinomycosis.

DISCUSSION

In the cases of abdominal actinomycosis following perforated peptic ulcers reported by Keynes (1924) and Shearburn (1943) the disease remained in the upper part of the abdomen. In the case reported here it occurred in the pelvis, and it is assumed that the organism must have been present in the free fluid in the abdomen as the result of the perforation. This is supported by the fact that the operation scars, and particularly the suprapubic drainage

wound, both showed signs of a chronic infection within a few weeks of the operation. The appendix, which was removed at the first operation, looked normal and is unlikely to have been the origin of the infection. The other possibility to consider is that the cystic right ovary was the primary actinomycotic lesion, but ovarian actinomycosis is usually considered to be due to transperitoneal spread from another focus, commonly from the ileocæcal region. The fact that the disease did not develop in the upper abdomen suggests that the duodenal lesion was not actinomycotic and that the organism was probably present in the stomach contents at the time of the perforation. It may be of significance that at the time of her perforation she was working at a farm, and although she had little direct contact with cattle she may have been infected from that source.

The recovery of the patient is almost certainly due to the penicillin therapy rather than to the iodine which was also given, and it is interesting to note that, even after 10·5 mega-units of penicillin had been given, the organism was found to be very sensitive to penicillin. It is reasonable to suppose that if the lesions in the paramedian scar were actinomycotic, they were cured by the curettage. This case also illustrates the prolonged treatment required to cure the disease and the report would be incomplete without a word of praise for the fortitude of the patient, who received almost 300 intramuscular injections of penicillin. It is probable that the diagnosis of actinomycosis in this case would have been made much earlier had the disease followed appendicitis rather than a perforated duodenal ulcer, and this report is published in the hope that similar cases in future might be more easily recognized.

SUMMARY

A case of abdominal actinomycosis following a perforated duodenal ulcer is reported.

The literature concerning similar cases is reviewed.

The origin of the infection in this case is discussed

The prolonged treatment with penicillin required to cure the disease is stressed.

I am greatly indebted to Professor Digby Chamberlain for permission to publish this case and for his many helpful suggestions; and also to the staff of the Bacteriology Department for their help in isolating the organisms and for numerous penicillin assays.

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MULTIPLE PERFORATED GASTROJEJUNAL ULCERS

BY D. J. LIVINGSTONE

GLASGOW ROYAL INFIRMARY

PERFORATION of a peptic ulcer is of such common occurrence, and operation for this condition so much a routine matter for the surgeon, that the warning that more than one perforation may be present at one time tends to grow dimmer as the months go by without producing an example to stimulate alertness.

Undoubtedly the simultaneous perforation of two or more peptic ulcers is uncommon, although Finney (1900) states that it occurs in 20 per cent of all cases of perforation—a figure which seems incredible in the light of present-day experience. Aird (1948) gives the incidence as less than 1 per cent, and Austin (1938) bears witness to the rarity of the condition, both from his own experience and from the scarcity of reported cases in the literature. In one surgical unit in Glasgow Royal Infirmary the number of perforated peptic ulcer cases treated during the last ten years was 334, of which only the case reported below was multiple.

A study of 33 cases collected by Masson and Simon (1927) shows that the diagnosis of the condition is usually made at autopsy, rarely at operation, and never clinically, and that the mortality is high. Of these 33 cases, only 18 came to operation, and only 4 had both perforations repaired. These 4 cases recovered.

In the case reported below the diagnosis was made at operation. The patient made an uneventful recovery.

As I have been unable to find a similar case among those reported in the literature, it will perhaps be of interest.

CASE REPORT

N. T., a male aged 37 years, was admitted to Glasgow Royal Infirmary on April 29,1948, at 7.30 p.m., suffering from severe epigastric pain which had started suddenly at 5 p.m. that day. For many years he had suffered from indigestion and had been in hospital in both 1933 and 1934 for medical treatment of duodenal ulcer. This treatment gave him only temporary relief, and after many exacerbations of his symptoms subtotal gastrectomy was performed in 1946. For nine months after operation he was relatively symptom-free, but pain and vomiting then recurred in increasingly frequent attacks up to the date of admission. These attacks, which were relieved by food and alkali, finally culminated in the severe attack of pain without vomiting, which led to his urgent admission to hospital.

The patient was very shocked, his temperature subnormal, and his pulse and respirations rapid. There was a cyanotic tinge of his lips, nose, and lobes of ears; his abdomen was rather tender and rigid throughout; liver dullness was absent.

A diagnosis of perforation of a peptic ulcer at the gastrojejunal anastomosis was made, and the patient was operated on at 9.30 p.m.

AT OPERATION.—Under light general anæsthesia with curare, the abdomen was opened through a right paramedian incision. Multiple adhesions in the epigastric region made the gastrojejunal anastomosis difficult to visualize, but when this was done a perforated ulcer was located on the posterior part of it. This was closed by a purse-string suture and an omental graft. On further exploration a lesion was noticed on one of the loops of small bowel, which when inspected proved to be a perforated ulcer of the jejunum 12–15 in. distal to the anastomosis and on the antimesenteric border. This was repaired with Lembert's sutures. Drainage was established in the rectovesical pouch and pouch of Morrison, and the abdominal incision closed.

The patient made an uneventful recovery. He was dismissed home on May 15, symptom-free, and had remained so one year after operation as long as he kept to a bland diet.

SUMMARY

A case of simultaneous perforation of a gastrojejunal and a jejunal ulcer is described.

Such cases appear from the literature to be uncommon, and diagnosis to be largely accidental even at operation.

Operative repair of the perforations was followed by uneventful recovery.

I wish to thank Mr. John Dunbar for permission to publish this case.

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OSTEOGENIC LEIOMYOSARCOMA OF THE BLADDER

BY H. MORUS JONES, M.C., AND C. F. ROSS

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SARCOMA of the bladder is a rare disease. The published cases were reviewed by Crane and Tremblay (1943) with especial reference to those producing bone. They reported a case of primary osteogenic sarcoma of their own, and collected 151 cases of sarcoma from the literature, of which only 8 were productive of bone or cartilage. Of these, 6 were regarded by them as primary osteogenic sarcoma.

This paper is concerned with the report of a further case of bladder sarcoma producing bone, and is of particular interest in that the patient gave a history of the removal of an osteogenic sarcoma of bone involving the lower end of the left femur sixteen years previously.

CASE REPORT

Mrs. A. P., aged 44 years, was admitted to Ashford Hospital under the care of Mr. E. N. Callum on Jan. 5, 1949.

HISTORY.—For the previous three months she had suffered from attacks of hæmaturia, and for three days before admission the hæmaturia had been profuse, with the passage of clots, and accompanied by frequency of micturition and dysuria.

Past History.—At the age of 29 years, in July, 1933, the patient had been admitted to St. Bartholomew's Hospital with a dull aching pain in the left knee of three months' duration. Clinical and radiological findings suggested the presence of a primary sarcoma of bone at the lower end of the left femur. Following a six-day course of pre-operative deep X rays, amputation just below the greater trochanter was performed by Sir Charles Gordon-Watson. The patient made a good recovery, and was discharged on July 28.

The specimen showed a lobulated tumour of the lower end of the femoral shaft, the cortical bone had been destroyed, and growth had invaded cancellous bone. Histologically it was reported as a well-differentiated osteogenic sarcoma, probably of low malignancy. (The specimen is in the St. Bartholomew's museum.)

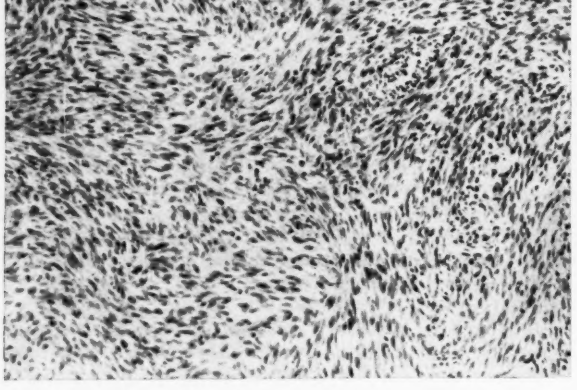

FIG. 355.—Leiomyosarcomatous part of the tumour. (× 72.)

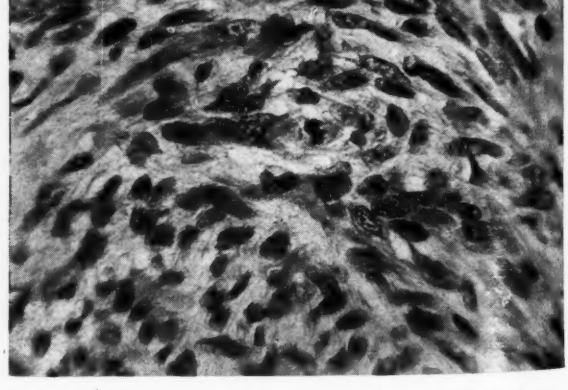

FIG. 356.—High-power view of part of *Fig.* 355, showing a cell in mitosis. (× 3.55)

ON EXAMINATION.—The patient was well nourished and putting on weight. Complete physical examination revealed no abnormalities except that there was a well-healed amputation stump of the left thigh. *Urine*: sp. gr. 1020; reaction, neutral to litmus; no reducing substances present; bile absent; protein, 160 mg./100 ml.; deposit, moderate numbers of red cells and a few pus cells; Culture, moderate growth of coagulase-negative *Staph. albus*. *Radiography*: No abnormality in the chest or abdomen. Urogram, normal. *Cystoscopy*: a pedunculated tumour in the upper part of the bladder. *Biochemical tests*: Blood-urea, 29 mg./100 ml.; serum alkaline phosphatase, 8 King-Armstrong units; hæmoglobin, 11·5 g./100 ml. (77 per cent).

TREATMENT.—Jan. 19, 1949: Fulguration with the cystodiathermy. Bleeding ceased and the patient was discharged on Feb. 4. On her return home the hæmaturia recurred, with a good deal of pain on micturition. The patient was re-admitted on March 2. March 4, 1949: Further cystoscopy was performed and the pedunculated tumour was again seen in the vault of the bladder. Because of the persistence of the hæmaturia after previous fulguration, it was decided to proceed forthwith with a suprapubic transvesical operation. A midline subumbilical incision was made and the bladder opened. A pedunculated tumour the size of a small walnut was found in the upper part of the bladder, but no other growths could be seen. The tumour was removed together with a portion of the mucosa and muscle of the bladder wall at its base. The bladder wound was closed around a suprapubic drainage tube, which was removed in four days' time. The patient made a good recovery and was discharged on March 21.

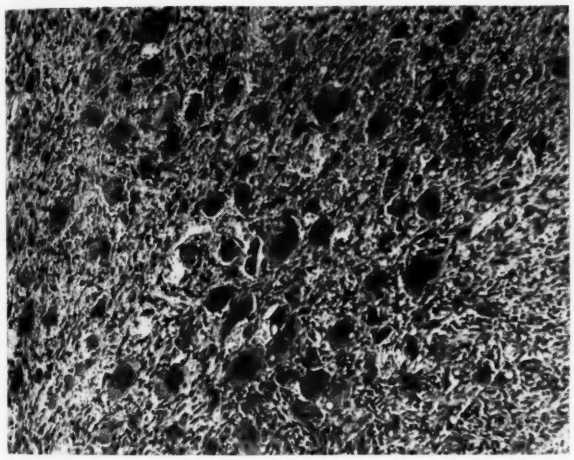

FIG. 357.—Osteoclastomatous part of tumour. (× 72.)

A preliminary pathological report of osteogenic sarcoma was given, and in view of this, and the past history of the removal of an osteogenic sarcoma of bone, a complete clinical and radiological examination of the whole skeleton was made. It failed to reveal the presence of secondary deposits. On clinical grounds, therefore, it was thought unlikely that this was a metastasis from the femur because of the length of time since the primary growth. Further, it seemed highly unlikely that secondary deposits should be confined to one nodule in the bladder. The patient has been carefully followed up since discharge. Cystoscopy was again performed in July, 1949, and no trace of tumour could be found. The patient has been seen as recently as June, 1950, and is quite well and free from urinary symptoms.

PATHOLOGICAL FINDINGS.—

Macroscopically, the tumour consisted of a slightly nodular mass of tissue 3 × 2 × 2 cm., with an irregular crusted surface covered with urinary salts. There appeared to be a short pedicle about 8 mm. wide, partly embedded in the mass. The cut surface showed pale tissue with areas of hæmorrhage and hard areas suggesting calcification or ossification (it was not possible to cut it with a knife).

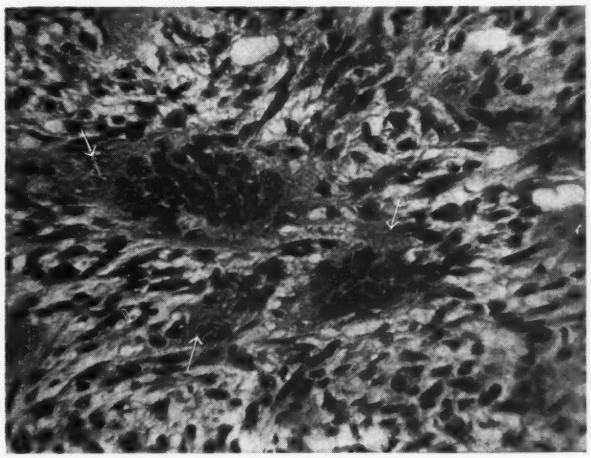

FIG. 358.—Osteoclast-like giant cells containing inclusions (indicated by arrows). (× 300.)

Microscopically (after decalcification), the pedicle consisted of chronically inflamed connective tissue which was highly vascular. It contained a few bundles of plain muscle cells, some of which were in mitosis. There was a good deal of œdema and hyaline degeneration of the collagen, with small foci of calcification here and there. Hæmosiderin-laden histiocytes were scattered throughout, and one or two small thrombosed arteries were seen. The base of the pedicle was quite necrotic, though some dubious tumour cells were present. Its surface was covered by chronically inflamed transitional epithelium which was continued for a short way over the main tumour mass, becoming thinned and ulcerated before disappearing. The bulk of the growth consisted of an intermingled mass of cells of varied morphology with areas where one or other cell type predominated, but mostly presenting the structure of a leiomyosarcoma, in which mitoses were fairly frequent (*Figs.* 355, 356). In places there was considerable admixture with multinucleated giant cells resembling osteoclasts, and in parts the characteristic leiomyosarcomatous tissue gave way to one much more like the spindle-celled stroma seen in

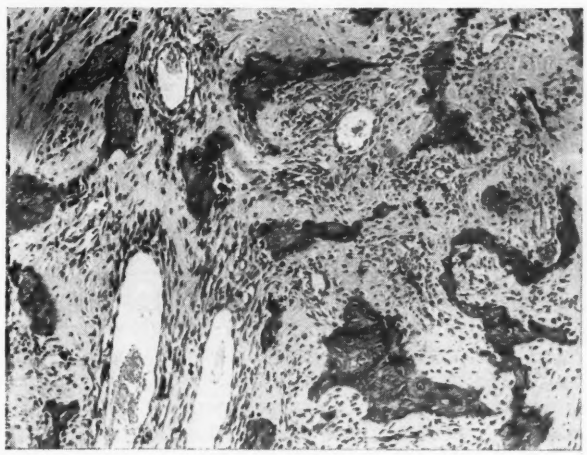

FIG. 359.—Bony part of the tumour. (× 72.)

osteoclastoma, and some areas mimicked this condition quite closely (*Fig.* 357).

Most of the giant cells contained elliptical or spicular isotropic refractile bodies which were unstainable by many common methods (hæmatoxylin, eosin, iron hæmatoxylin, van Gieson's stain, Mallory's stain, Weigert's elastic tissue stain, von Kossa's method for calcium in frozen sections) nor gave a positive periodic-acid-Schiff reaction. Micro-incineration was not possible and the nature of the material remains a mystery (*Fig.* 358). These areas merged into masses of osteoid tissue and in the middle of the tumour was well-formed woven bone (*Fig.* 359). Mixed up with the latter were malignant

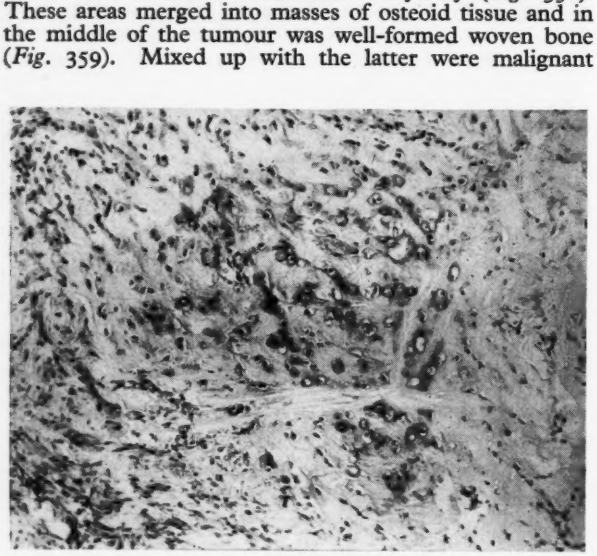

FIG. 360.—Primitive cartilage. (× 72.)

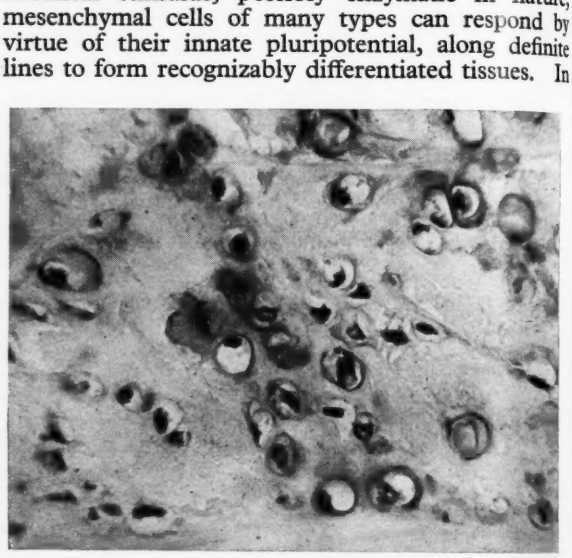

FIG. 361.—Primitive cartilage. (× 300.)

plain muscle cells and fibroblasts. Collagen was present and permeated the tumour mass in varying amounts, with quite thick trabeculæ here and there. In one area was some primitive cartilage (*Figs.* 360, 361) well shown by staining with acid Giemsa. Throughout the tissue were cells of indeterminate nature often appearing to be transitions between one or other of the more differentiated cells. The surface of the mass was covered by necrotic tissue containing masses of pus cells merging into chronically inflamed granulation tissue, which, in turn, merged into the main mass.

DISCUSSION

At first sight, the tumour described above was thought possibly to be a primary osteogenic sarcoma of the bladder or a long delayed metastasis from the osteogenic sarcoma of the femur. The finding of definite plain muscle tissue of a malignant nature ruled out these possibilities, however, and it was concluded that the tumour was, in fact, a leiomyosarcoma which was producing bone. This was the majority opinion of the Consultant Panel in Morbid Histology of the Pathological Society.

The question of how bone comes to be produced is ill understood. It had been shown by Neuhof (1917) that fat or fascia transplanted into the bladder of dogs ossified, and Huggins (1931) showed that urinary epithelium stimulated bone formation if transplanted into subcutaneous tissue or fascial sheaths. It is also known that heterotopic bone occurs in suprapubic scars, particularly after bladder operations, and it seems not unreasonable to suppose that bone might form in relation to tumours in the bladder itself, though Crane and Tremblay (1943) found that this occurs very infrequently. Bladder epithelium has a high alkaline phosphatase activity and it seems very likely that this plays a part in such bone formation.

As Harwell Wilson (1941) pointed out, ossifying tumours of extraskeletal tissues may occur practically anywhere in the body, though, next to muscle, breast and thyroid seem to be the commonest sites. It appears difficult to avoid the view that under a chemical stimulus, possibly enzymatic in nature, mesenchymal cells of many types can respond by virtue of their innate pluripotential, along definite lines to form recognizably differentiated tissues. In the present case the diversity of the cell structure was quite remarkable, and the presence of intermediate cell types made it seem not improbable that one was dealing with the phenomenon of mesenchymal metaplasia. In this connexion, the reader is referred to the views of Nicholson (1923) and of Willis (1948).

The main features of bladder sarcoma as described by Crane and Tremblay are as follows: The initial symptom is hæmaturia; dysuria and frequency of micturition come later. The tumour may be localized or diffuse, polypoid or pedunculated, and the majority are leiomyosarcoma. Clinically a diagnosis of 'bladder tumour' is made, and the diagnosis of sarcoma rests on the histology.

The case reported presents some of these features, but is also unusual in that it is a case of two different types of sarcoma occurring in the same individual. The prognosis appears to be good, the patient being alive and well with no evidence of recurrence or metastasis nine months after a conservative type of operation. This is contrary to the course of events in most types of bladder sarcoma, which grow rapidly and infiltrate deeply, most cases showing a fatal issue within three months.

Following on the report of sarcoma, the question arose as to whether further operative procedure of a more radical nature was necessary. However, in view of the general good health of the patient and the absence of symptoms, it was decided to adopt a policy of 'watch and wait' and close follow-up. Should there be a recurrence, total cystectomy is contemplated, in the absence of demonstrable secondaries.

Summary.—A case of leiomyosarcoma of the bladder is described which was productive of bone. The clinical and pathological features are described and discussed.

Our thanks are due to Mr. E. N. Callum for permission to report this case; and to Professor W. D. Newcomb, who gave valuable assistance in criticizing the report. Mr. R. M. Vick, Sir Charles Gordon-Watson, and Dr. G. J. Cunningham made available the original findings at St. Bartholomew's Hospital. To them and to Professor Sir James Paterson Ross, Professor R. Scarff, and the Consultant Panel in Morbid Histology, we tender thanks for their aid; also to E. N. Targett, F.I.M.L.T., who helped with the photomicrography.

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OSSIFYING HÆMANGIOMA OF THE CEREBRUM

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CALCIFICATION in or around cerebral hæmangiomata is not uncommon. Ossification is rare. Mattaushek (quoted by Stief, 1924) reported a case, and Weiss (1933) a similar example. Weiss's patient was a female, aged 22, with a hæmangioma in the region of the septum pellucidum associated with persistent

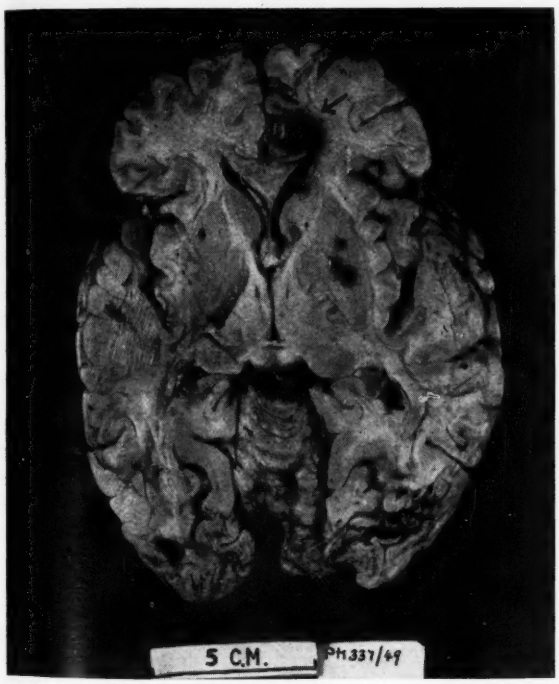

FIG. 362.—Macroscopic view of brain. The arrow indicates the lesion. The cysts in the right putamen are also visible.

headache and blindness in one eye. She died of pneumococcal meningitis following operation.

The example to be described occurred as an incidental finding in a middle-aged female subject who died of hypertensive cardiac failure and bronchopneumonia.

CASE REPORT

The patient was a female aged 54, employed as a kitchen-hand. For a year before admission to hospital she suffered increasing lassitude, weakness, and headache.

ON ADMISSION (Nov. 1, 1949).—She was dyspnœic and cyanosed. The blood-pressure was 240/130. The apex-beat was in the 5th intercostal space in the left anterior axillary line. Pulsus alternans was observed. Extensive crepitations were heard in the lungs. There was œdema of the ankles, sacral region, and hands. Bilateral papillœdema was present, also hæmorrhages and exudates in the retinæ.

TREATMENT with mersalyl, digitalis, venesection, salt-free diet, oxygen, morphine, and cardophyllin were of little avail. The patient went steadily downhill and died on Nov. 7, 1949.

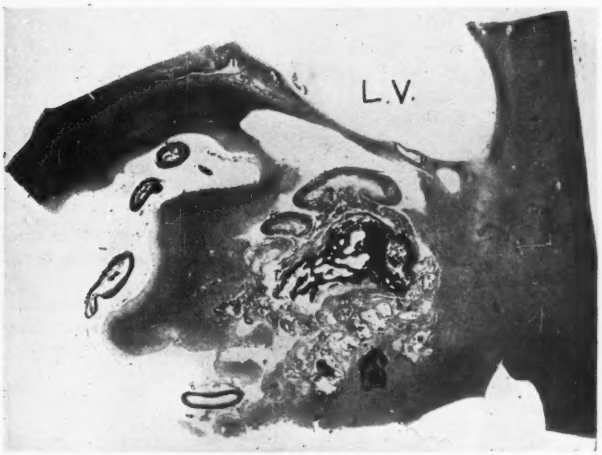

FIG. 363.—The lesion, which lies anterior to the lateral ventricle (L.V.). (H. and E.) (× 3·3.)

MAIN AUTOPSY FINDINGS.—The body was 5 ft. in length and weighed 55 kilos. There was moderate œdema of the lower limbs and sacral region. The heart weighed 565 g. The left ventricular wall was markedly hypertrophied. All four chambers were dilated. Antemortem thrombus was present in the right auricle. There was generalized arterial hypertrophy and moderate atheroma. The lungs were œdematous and showed many areas of bronchopneumonia, also a few small scattered peripheral infarcts. The kidneys were small and granular, with reduction in the width of the cortex. Together they weighed only 130 g. The liver showed centrilobular congestion and weighed 1300 g. A minute hæmangioma was present in the right lobe of the liver.

The brain weighed 900 g. Externally there was no abnormality except moderate atheroma of the cerebral arteries. Section of the brain revealed a curious lesion

in the right frontal lobe, immediately anterior to the lateral ventricle and abutting on to the median fissure. It was a well-demarcated, partly fibrous, partly ossified, partly vascular 'tumour', 1·5 cm. in diameter, supplied with delicate twigs from the right anterior cerebral artery. Two cysts of cerebral infarction were present in the right putamen. Microscopically, the lesion in the frontal lobe consisted of cavernous blood spaces, lined with endothelium, together with hyaline fibrous tissue, fibrosed arteries and veins, as well as smaller vessels, and bone. At the periphery there was a zone of glial and fibrous connective tissue. Many of the microglia in this zone contained hæmosiderin. Some of the bone seemed to lie within what was once the lumen of fairly large blood-vessels, suggesting deposition in organized thrombus.

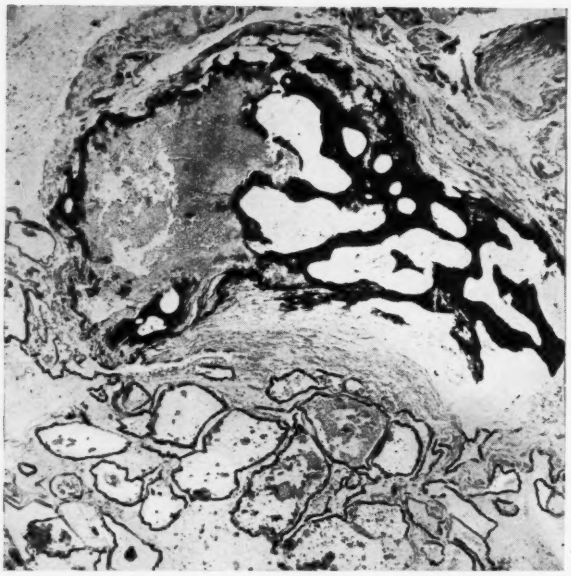

FIG. 364.—The lesion. The bone is apparently intravascular. (H. and E.) (× 15.)

It was mainly lamellar bone, but a little woven bone was also present. Osteoblasts were seen, but osteoclasts were absent. The marrow was fatty.

The presence of bone does not alter the view that with doubtful exceptions all angiomas of the nervous system are developmental vascular hamartomas.

COMMENT

Hypertension was clearly so dominant a clinical feature in this case that extraordinary investigations were unnecessary. Supposing, however, that the patient had presented herself with a headache of obscure origin, then radiographic examination of the skull might have led to some difficulty. The finding of opacity caused by the bone would have demanded a consideration of the causes of calcification in and around the cerebrum. These causes include neoplasms, tuberculomata, parasitic affections, angiomatous malformations, and intracranial aneurysms.

Calcification occurs in about 20 per cent of all gliomas, scattered diffusely or limited to one small area of the tumour. The distribution of the calcification usually gives a characteristic radiological pattern in oligodendroglioma and sometimes in astrocytoma, but in many cases it does not indicate the type of tumour. Calcification may occur in ependymomas.

Meningiomas may show diffuse or localized calcification. This may also be present in cholesteatomas and teratomas. Metastatic neoplasms are not calcified, with the rare exception of osteogenic sarcoma. Chronic cases of tuberculoma may show calcification. In cysticercosis, scattered calcified

FIG. 365.—Detail of bone, which is mostly inactive lamellar bone with fatty marrow. (H. and E.) (× 120.)

cysts are sometimes seen in the brain. In hydatid disease, one or more calcified cysts may be found in the cerebrum, but death usually occurs before calcification. The necrotic material in toxoplasmosis may contain patches of calcification. Intracranial aneurysms sometimes have calcified walls. Angiomatous malformations may be associated with calcification of the adjacent brain. Sometimes tortuous lines of calcification are visible.

SUMMARY

A case of ossifying hæmangioma of the cerebrum is described. It occurred in a woman aged 54. No symptoms apparently were caused by the lesion. The differential diagnosis of calcified lesions of the cerebrum is discussed.

I wish to thank Dr. J. W. Litchfield for permission to publish this case; Professor W. D. Newcomb and Dr. Merlin Pryce for their encouragement and criticism; and Dr. E. Neumark for German translations.

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AN UNUSUALLY LARGE LEIOMYOMA OF THE STOMACH

By A. S. RAJASINGHAM and G. H. COORAY, Colombo, Ceylon

Although leiomyoma has been generally recognized as the most frequent type of non-malignant gastric neoplasm, tumours of such large size as the one to be reported have seldom been recorded. Von Erlach is said to have successfully resected a 5400-g. tumour in a 36-year-old female (Golden and Stout, 1941). Willis (1930) recorded a subserous gastric myoma weighing 900 g. In our case the tumour weighed 4080 g. However, leiomyomata of very small size are not infrequent incidental findings at autopsies (Golden and Stout, 1941 ; Meissner, 1944).

CASE REPORT

A Sinhalese female, aged 45 years, was admitted to the General Hospital, Colombo, on May 6, 1949, complaining of a mass in her abdomen of five years' duration which had gradually grown to its present size. Apart from a loss of appetite and discomfort due to its size, there were no ill effects.

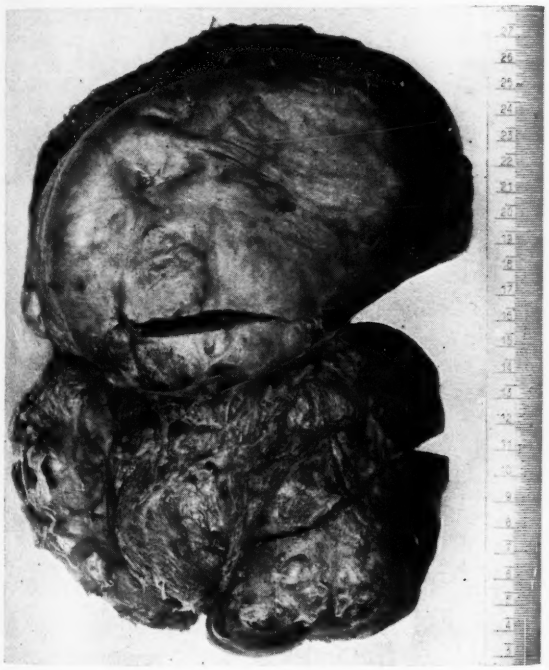

Fig. 366.—Large tumour separated into upper and lower lobes by a groove. Vascular adhesions on surface of upper lobe.

On Examination.—She was found to be rather emaciated. A large solid oval bi-lobed tumour, which showed a certain degree of lateral mobility, occupied the hypogastrium and epigastrium. Vaginal examination revealed a small retroverted uterus unattached to the tumour. As the nature and exact site of the tumour were obscure, an exploratory laparotomy was decided on.

At Operation.—On opening the peritoneal cavity by a long paramedian incision, a large encapsuled solid growth, constricted in its middle, was found arising from the greater curvature of the stomach. The serous coat of the stomach was stretched over the tumour and the muscle-coat was seen underneath it, gradually merging into the tumour substance. The omentum was adherent to the tumour and large blood-vessels passed over it. The liver appeared normal and no secondary deposits were found anywhere in the peritoneal cavity. The tumour was excised from its attachment to the stomach, leaving a small button-hole in the stomach mucosa, which was closed.

Convalescence was uneventful. The patient when last seen in September, 1949, was found to be quite healthy.

Description of Tumour.—The massive growth measured 23 cm. × 16 cm. × 13 cm. and weighed 4080 g. It was lined superficially by the serous coat of the stomach and was composed of an upper and lower lobe separated by a groove (*Fig.* 366). Numerous vascular adhesions were seen on the upper lobe, while the lower lobe showed but a few vessels, which probably explains the difference in appearance of the cut surfaces of the two lobes. The upper lobe presented a hard, greyish-pink whorled appearance, whereas the lower lobe contained semi-fluid necrotic tissue (*Fig.* 367).

Fig. 367.—Cut section of tumour viewed from above, showing the difference in appearance of the two lobes.

Histology (*Figs.* 368, 369).—The tumour was composed of interlacing bundles of spindle-shaped smooth-muscle cells with rather hyperchromatic nuclei. The cells were in the main fairly uniform in size, shape, and tinctorial characteristics.

Examination of several sections from different parts of the growth failed to reveal any mitotic figures. The supporting stroma consisted of collagen and reticulin fibrils, the latter passing between individual cells (*Fig.* 370). Deposits of calcium were seen in patchy areas

in the tumour tissue (*Fig.* 371). The greater part of the lower lobe showed areas of necrosis.

FIG. 368.—Low-power view, showing interlacing bundles of smooth-muscle cells. (H. and E.) (× 52·5.)

FIG. 369.—High-power view, showing closely packed smooth-muscle cells. (H. and E.) (× 260.)

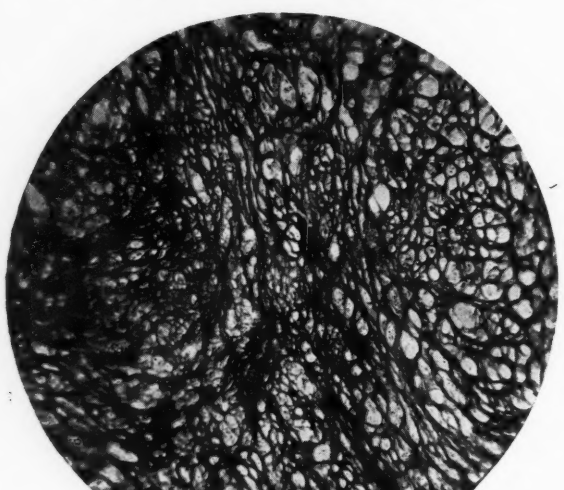

FIG. 370.—Arrangement of reticulin fibrils. (Silver impregnation.) (× 170.)

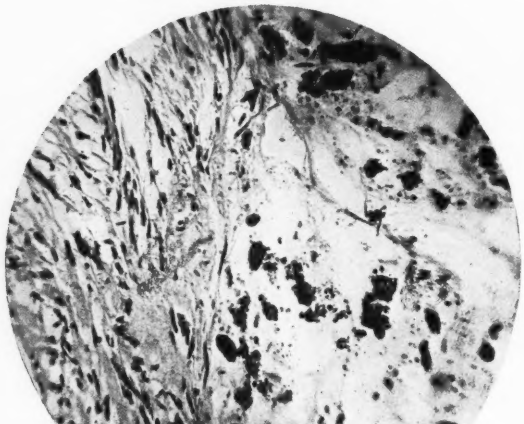

FIG. 371.—Calcium deposits in tumour. (H. and E.) (× 200.)

Discussion.—It was not possible to determine the nature of the tumour and its exact site of origin, clinically. The tumour filled almost the whole abdomen and appeared to arise from the pelvis. In spite of its enormous size, it was not considered malignant, a conclusion strengthened by the long history, easy mobility of the tumour within the abdominal cavity, and the absence of ascites. Its site of origin from the wall of the stomach was determined only after laparatomy. The tumour was growing away from the lumen of the stomach towards the serous coat—the so-called exogastric type (Golden and Stout, 1941). This type differs from the endogastric type where growth occurs towards the gastric mucosa, which not infrequently undergoes ulceration. Lack of symptoms such as those following ulceration and obstruction in this case is also accounted for by the direction of its growth.

Histologically the tumour was a typical leiomyoma, and in its structure did not differ from that of smooth-muscle tumours in other parts of the body. It resembled leiomyomata in other situations in respect to the types of degenerative changes. One lobe was almost entirely necrotic, while the other showed preservation of its structure—a difference which could be explained by the different degrees in the vascularity of the two lobes.

SUMMARY

A case is reported of a large gastric leiomyoma, weighing 4080 g., which was successfully removed. The histological features of the tumour are described.

Although gastric leiomyomata of such large size are infrequent, the condition should be kept in mind when confronted with a large abdominal tumour.

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REVIEWS AND NOTICES OF BOOKS

The Closed Treatment of Common Fractures. By JOHN CHARNLEY, B.Sc., M.B., F.R.C.S., Assistant Honorary Orthopædic Surgeon, Manchester Royal Infirmary; Visiting Orthopædic Surgeon, The Park Hospital, Davyhulme; Lecturer in Orthopædics, Manchester University; Late Hunterian Professor, Royal College of Surgeons. $6\frac{3}{4} \times 9\frac{3}{4}$ in. Pp. 190 + xii, with 133 illustrations. 1950. Edinburgh: E. & S. Livingstone Ltd. 35s.

IN *The Closed Treatment of Common Fractures* Messrs. E. & S. Livingstone have yet another winner to add to their list of successes. Because Mr. Charnley has so graphic a style and because of the importance of what he says, there is no better way of describing the scope of the book than by quotations from the Preface :—

". . . written primarily for the resident casualty surgeon . . . younger men whose practical knowledge cannot match their theoretical knowledge". "It is possible for such casualty officers to be fully conversant with modern text-books of fracture treatment and yet be unable with any degree of certainty to reduce many of the simple fractures. I believe that this follows from the fact that in many large text-books the space devoted to the detailed description of technique in the treatment of the common fractures is disproportionately small. An important step, on which might depend the whole success of a reduction, can be overlooked if it is concealed within one sentence".

". . . endeavoured to describe in detail what I consider to be the essential steps in the closed reduction of the common fractures, and at a length proportionate to the importance of the matter. No attempt has been made to write a comprehensive text-book, but by emphasizing various mechanical features common to the reduction of certain fractures (which might almost be regarded as 'principles') it is hoped that the student may learn to apply these to the successful reduction of rare fractures whenever he encounters them."

"*The ease with which perfect reductions can be obtained by closed methods when the injury is fresh, makes it especially important that the casualty officer should be skilful enough to take full advantage of being on the spot when the patient is first admitted to hospital.*" (Reviewer's italics.)

"It should be the aim of a good manipulative surgeon to know that a fracture has been reduced by his sense of touch without utter dependence on X-ray; it is possible to acquire this faculty for the Pott's, Colles', supracondylar fracture of the humerus, and the Bennett's fracture with some degree of certainty."

". . . an attempt is here made to re-emphasize the non-operative method, and to show that far from being a crude and uncertain art, the manipulative treatment of fractures can be resolved into something of a science."

Mr. Charnley succeeds in his aim brilliantly, convincingly, and with a lucidity many will envy. Herein are described and illustrated all those "tricks", wrinkles, dodges, and manœuvres which those who employ closed methods successfully—and there are many still doing so despite the appeal of nails, plates, and screws—employ consciously or unconsciously. Mr. Charnley has rendered a very great service to our patients by the manner in which he has emphasized them. There are other and larger books written about the treatment of fractures, but none so vital as this. There is not one of the 190 pages; there is hardly a sentence; and there is not an illustration (of which there are 133) which the reader will not want to underline because of its importance, and it is suggested that these remarks apply not only to resident casualty surgeons. It is believed that every orthopædic and traumatic surgeon in Great Britain and elsewhere will agree that this book has something to teach him. There are also two chapters containing first-class original matter, the reading and re-reading of which will well repay time spent—they are Chapter II, called "Joint Movement in Conservative Methods"; and the last chapter, on the walking calliper.

Cerebral Angiography. By P. ALMEIDA LIMA, Lisbon. With an Introduction by EGAS MONIZ. Foreword by Sir HUGH CAIRNS. $6\frac{1}{8} \times 9\frac{3}{4}$ in. Pp. 221 + xiv, with 181 illustrations. 1950. London: Oxford University Press. 45s.

ALTHOUGH cerebral angiography has been practised for several years in many neurosurgical clinics, yet it may be said its use is not widely appreciated.

Professor Lima, who has been a pioneer in this field, has published the first systematic work on cerebral angiography in this country. Working in Lisbon with Professor Egas Moniz, he has now more than 2000 cases to his credit and this must be the largest series in the world.

Lima's technique consists in injecting 8 c.c. of thorotrast (colloid suspension of 20 per cent thorium dioxide) into the common carotid artery. The injection is performed under local anæsthesia, and both sides are injected one after the other. Radiographs are taken at 2-second intervals so as to obtain an arteriogram and two phlebograms. The whole operation can be completed in fifteen minutes in the Out-patient Department and the patient is ambulatory and can return home the same day.

This book is beautifully illustrated with excellent radiographs ranging from the normal to the various pictures obtained from the different types of tumour formation within the cranium.

This monograph will be of value not only to neurologists and neurosurgeons, but also to anatomists and physiologists who wish to know more about the cerebral vessels and cerebral circulation.

An excellent production on a fascinating subject.

Cytologic Diagnosis of Lung Cancer. By SEYMOUR M. FARBER, M.D., MILTON ROSENTHAL, M.D., EDWIN F. ALSTON, M.D., MORTIMER A. BENIOFF, M.D., and ALLEN K. MCGRATH, jun., M.D., from the University of California Medical Service and San Francisco Department of Public Health. $8\frac{1}{2} \times 11$ in. Pp. 60 + xii, with 60 coloured illustrations. 1950. Springfield: Charles C. Thomas. (London: Blackwell Scientific Publications Ltd.) 45s.

THIS special monograph deals with a subject which is comparatively new and yet one which is of the greatest importance considering that malignant disease of the lung is on the increase. At the opening of the present century carcinoma of the lung was considered to be a rare disease. To-day it is one of the commonest forms of cancer, especially in men, and it is estimated that 15,000 patients in the United States of America die of bronchogenic carcinoma every year.

This book sets out the technical details for the study of cell detail with wet smears. It is well written and the facts are summarized in a lucid style. At the end of the book there are some ten beautiful coloured plates showing high-power magnification of malignant cells in sputum.

There can be no doubt that this book will be of inestimable value not only to the physician but also to the chest surgeon who is confronted with the treatment of malignant disease of the lung.

Chirurgie artérielle. Techniques, Indications, Résultats. By G. ARNULF, Nancy. With a Foreword by Professor RENÉ LERICHE. 6½ × 9¾ in. Pp. 248 + viii, with 79 illustrations. 1950. Paris: Masson et Cie. 1200 fr.

THIS monograph by a pupil of Professor Leriche is an able presentation of our knowledge of arterial surgery at the present time. The indications, technique, and results which may be expected from arterial ligation, suture, intubation, grafting, and anastomosis are described, and there are also chapters on embolectomy, arteriectomy, and endarteriectomy. Professor Arnulf writes with an exceptionally logical and lucid style and his illustrative cases give a sense of reality to some of the more uncommon vascular operations which the majority of surgeons are not often called upon to perform. Good reasons and statistics are submitted to show what may be expected from these procedures which, though technically exacting, need not be regarded as surgical acrobatics. The book is essentially one on the operative surgery of arteries and veins and does not describe in a wider sense the management of cases of peripheral ischæmia due to arterial disease. Ganglionectomy and infiltration of sympathetic trunks are mentioned only in relation to ligation of main arterial trunks, though periarterial sympathectomy is given a full chapter. The author admits that the physiological basis of this operation is in doubt but still considers that as a minor procedure it is a legitimate and valuable one for a variety of conditions.

The surgery of the aorta and congenital lesions of the heart is described and the French statistics are given up to 1948 for these conditions. The book is completed by a brief but detailed chapter on the use of anticoagulants—continuous infusion of heparin is preferred and it is evident that dicumarol is regarded with reason as a dangerous drug.

To any surgeon interested in arterial surgery this book will give many valuable ideas and a mass of factual information well supported by an extensive bibliography.

Operative Surgery. By FREDERICK C. HILL, B.A., M.S., M.D., Associate Professor of Surgery, The Creighton University School of Medicine, Omaha, Nebraska. With a Foreword by CHARLES W. MAYO. 6 × 9¼ in. Pp. 698 + xiv, with 255 illustrations. 1949. New York: Oxford University Press. 63s.

As the writer of the Foreword states, "when a reputable and recognized surgeon undertakes the task of writing a book on surgery, he undoubtedly does so with the feeling that he is filling a need", and, again, "once one has selected the profession of medicine as a life's work, however, in the same breath has one assumed the responsibility of life-long study, despite the quantity of active experience one has enjoyed".

The need the author claims to have filled, is to provide one volume wherein "the gross appearance of surgical lesions is described, the proper treatment is indicated, and detailed description of operative procedures is given". The book is purely one on operative surgery, but the macroscopical pathology of conditions found at operation is described.

He urges all through that as far as possible the gross pathology of the whole body should be considered before adopting any particular procedure, e.g., the abdomen should always be opened with a perfectly open mind, and the incision be sufficient to explore thoroughly and not merely to take out an appendix in a record time and leave much more gross and serious pathology behind. Each chapter is prefaced by the points considered to be of importance in the subsequent pages, and even a cursory study of these by the reader is sufficient to remind him of general principles in pre-operative and post-operative care, and also of possible accompanying pathological conditions which otherwise he might forget.

The first three chapters are devoted to general considerations, such as pre-operative treatment, ligature materials and their uses, and instruments. Then follow in sequence chapters arranged on a regional basis. Each chapter is divided into three parts, viz., the differential diagnosis of the most common lesions that may be found with their pathological basis, then the suggested treatment, and finally the technique advised in the operation, with a brief reference to the post-operative care, a complete chapter being devoted to the latter at the end of the book.

In this age of super specialism it is very easy to criticize one's own particular pet operation as it is described in a single-volume text-book of operative surgery; or disagree with the particular operation which appeals to the author.

To take various samples at random, there are few surgeons who would wish a patient to come round from a general anæsthetic after one lobe of a thyroid had been excised, in order to hear him speak so as to be sure the recurrent laryngeal nerve had not been injured and then re-anæsthetize him and proceed with the other lobe. Others would prefer to divide the ureter early in doing a nephrectomy so as to enable the pedicle to be more easily approached. The author divides it after the pedicle has been secured, nor does he advocate removing the last rib to get more room for the procedure.

Some would disagree that it was necessary to do a jejunojejunostomy if the anterior Polya method of gastrectomy had been adopted.

The "old fashioned" two- or one-stage suprapubic prostatectomy does not appeal to the modern urologist, yet all will agree that they were good and comparatively safe procedures. Even some of the ultra-modern methods of prostatectomy occasionally end up with a suprapubic removal and drainage.

The reader is impressed with the honesty of the author. He describes the technique he has found to be most uniformly successful, and there is no doubt that he is a very safe surgeon, which attribute appeals more to the patient and reviewer than the slick and brilliant operator.

The publishers are to be congratulated on the format and type of the book. The illustrations are excellent and it should be welcomed and valued by all house surgeons and those in training for a surgical career. The style of the writing is such as to give it a permanent place in the surgical library of a general surgeon.

The author's claim in the Preface that "although good surgical judgement is gained primarily by training and experience, there are many principles, well known to the mature surgeon, that can be explained to the advantage of the younger man", justifies the need which he felt would be filled by writing this book.

An Introduction to Pathology. By G. PAYLING WRIGHT, D.M., F.R.C.P., Professor of Pathology, Guy's Hospital Medical School, University of London. 5⅞ × 8¾ in. Pp. 569 + x, with a large number of illustrations. 1950. London: Longmans Green & Co. Ltd. 30s.

PATHOLOGY is now a large branch of medicine and becomes more important as the years pass by. Pathology invades every branch of medicine, surgery, and gynæcology. Medical students having passed their anatomy and physiology examination begin their clinical studies with little knowledge of pathology. There is a definite hinterland between the normal and the abnormal; some may call this physiological pathology, while others pathological physiology. Professor Payling Wright has written a book which covers this hinterland and also sets out the main principles of disease processes, laying special emphasis on aetiology and pathogenesis. This is just

what the medical student requires, for he cannot assimilate any surgical pathology unless he has a sound knowledge of general pathology.

The author's mature experience has made it possible for him to place more stress on pathological processes as aspects of disturbed physiology than on the structural changes that take place in the tissues.

The book is well written and the illustrations are excellent and the references adequate.

The ideal book on pathology for the medical student.

Surgical Urology. By Dr. G. de ILLYES, Professor of Urology and Director of the Clinic of Urology in the Hungarian Royal Peter Pázmány University, Budapest. In 2 volumes. $9\frac{5}{8} \times 6\frac{5}{8}$ in. Pp. 679, with 391 illustrations, a number in colour. 1948 (1942). London: Constable & Co. 63s. net.

PROFESSOR ILLYES is so well known by urologists throughout the world that any book coming from his pen is bound to be received with respect and interest. The publication of this two-volume text-book was delayed by the outbreak of war; it was printed in Hungary during the war and is extensively illustrated by original drawings and photographs. Some of the latter are not of such clarity as to warrant their inclusion, although they are evidence of the vast amount of clinical material which passes through the Urological Clinic of the University of Budapest. The teaching throughout is sound and differs little from that of this country. There are some deficiencies due to the period between completion and publication, and the treatment of malignant disease of the bladder does not come up to modern standards. The book, however, contains so much of good sense and practical value that every urologist should read it; allowance must be made for the Continental idiom.

The Mechanism of Abdominal Pain. By V. J. KINSELLA, M.B., Ch.M. (Sydney), F.R.C.S. (Eng.), F.R.A.C.S., Hon. Surgeon, St. Vincent's Hospital, Sydney. $9\frac{3}{4} \times 5\frac{7}{8}$ in. Pp. 230 + xiv, with 17 illustrations and 8 plates. 1948. Sydney: Australasian Medical Publishing Co. Ltd. 32s. 6d.

OUR present knowledge of visceral pain consists of a mixture of observation, theory, and conjecture, and this volume by Mr. V. J. Kinsella provides a survey of all three. The value and chief merit of the book lies in the careful account of Kinsella's own observations over the past twenty years. Kinsella has always made plain that pain investigation can only be carried out satisfactorily in man, and now presents in one volume the results of his surgical opportunities.

In a subject so clouded by speculation it is perhaps no longer useful to report afresh the old and confusing theories of visceral pain and pain mechanisms, but the historical account does provide opportunity to show four beautiful reproductions from the works of Vesalius, Eustachius, and Willis. Kinsella goes on to describe the precision and care with which the observations on visceral sensibility are made. He notes that the mesentery is acutely sensitive to painful stimulation, and that pain is evoked by pressure on an inflamed viscus. He accepts, therefore, on good evidence, the fact of direct visceral sensitivity when the viscus is inflamed. His explanation, however, of the increased sensitivity of the mesentery compared with the viscus, as being due to an increased concentration of pain fibres in the mesentery, will not satisfy those who have attempted to test this quantitative view by experiment.

Tenderness in visceral disease is thus explained as due to tenderness of inflamed visceral tissue. This is an important observation in clinical surgery. "The viscus, apparently tender on physical examination, is tender, in fact . . . . . The pathways of diagnosis will be made easier when visceral sensibility is freed from the shackles of indirect mechanisms." To direct visceral tenderness Kinsella would add an extra factor in localization, the "local sign"—that is to say, the patient adds to the sensation of tenderness on pressure, the knowledge of which part of the body wall was pressed upon, so localizing further the region of the painful stimulus.

Kinsella stresses once again that a poorly localized pain is not a "referred" pain, and that visceral pain is a deep internal pain and is not referred or localized to the body wall, or depends in any way on a cutaneous link. At the same time he accepts the view that pain impulses arising from the viscera can, under certain conditions, overflow into a somatic area, thus perpetuating the idea of the "irritable focus" in the cord, for which in fact he offers little evidence.

Cutaneous hyperalgesia in the presence of visceral disease is accepted as an inconstant and variable finding, and explained on the basis of an emotional response to pain and anxiety, which sets up a discharge of impulses in the fibres of the autonomic nervous system supplying the vicinity of the painful area. These in turn produce changes in the skin of an electrochemical nature, with liberation of P-substance (of Lewis). Kinsella believes this process to be a remnant of our phylogenetic past! This view is further developed in a chapter on the visceral neuroses.

It is disappointing to find only cursory treatment of the important and still debated subject of abdominal rigidity. Kinsella holds that rigidity of the anterior abdominal wall can arise from stimulation of the anterior parietal peritoneum (as after perforation of a peptic ulcer), or from purely visceral stimulation (as in biliary colic), although the former is the more potent. This double mechanism may be true, but convincing evidence is still to be sought.

Kinsella's observations lead him to believe that the adequate stimulus for visceral pain is compression of nerve-fibres in the wall of the viscus, which is more sensitive to this stimulus when inflamed. He recognizes, too, the sensibility of the anterior parietal peritoneum, but considers only briefly the sensibility and localization of pain from the posterior parietal peritoneum—a still neglected problem.

In an excellent chapter on the pain of peptic ulcer Kinsella examines critically the two opinions that pain is due to acid acting on sensory nerve-endings exposed in the ulcer, or to muscle tension, and comes to the conclusion that neither explanation is in accordance with observed facts. His own view is that the pain is due to vascular tension in an inflamed tissue. This chapter affords a splendid example of that intellectual process in natural philosophy which contemplates known facts and then synthesizes them into a new conception.

If at times Kinsella's conclusions and speculations tend to outstrip the evidence on which they are based, it is not to deny that this is a thoughtful and scholarly book, provocative of further thought and argument, and one to be read and considered by all who are concerned in the intriguing problem of visceral pain.

Handbook of Surgical Urology. For Internes, Hospital Corpsmen, and Nurses. By NELSE F. OCKERBLAD, M.D., F.A.C.S., Professor of Clinical Urology, University of Kansas School of Medicine. $5\frac{1}{4} \times 7\frac{1}{2}$ in. Pp. 189 + viii, with 52 illustrations. 1949. Baltimore: The Williams & Wilkins Co. (London: Baillière, Tindall & Cox.) 31s. 6d.

THIS small book differs from many of its class in that it is a pleasure to read it. The first chapter alone on the "History of the Speciality of Urology" is calculated to arouse the keen interest of any student or newly-appointed house surgeon in his subject. Another good section is that on the "Care of Urological Instruments"; mercuric

cyanide is advocated as a sterilizing agent for cystoscopes and woven catheters, but the strength is not indicated. The author's own nephrectomy table is pictured, and obviously has many advantages.

Preparation and after-care, sulphonamides and antibiotics, and diet in urology all receive adequate attention, but the chapter on " Urological Surgery " suffers somewhat by the condensed lists of operations; possibly they will be helpful to the nurse, and she will certainly pick up much useful knowledge from the book as a whole. " Some persons begin to complain about their bowels the minute they get to a hospital ", is an example of the forthright and practical style in which the book is written.

Non-gonococcal Urethritis. By A. H. HARKNESS, M.R.C.S., L.R.C.P., Joint Director of the Endell Street Clinic, St. Peter's and St. Paul's Hospitals (Institute of Urology); etc. $6\frac{7}{8} \times 9\frac{5}{8}$ in. Pp. 424 + xii, with 167 illustrations, 73 in colour. 1950. Edinburgh: E. & S. Livingstone Ltd. 52s. 6d.

FROM time to time it is our pleasure to review in these columns a book on some special subject which is of such merit as to constitute a landmark in our knowledge of disease and to evoke a feeling of pride that it has been written in the English language. Of those published in recent years we would mention Watson-Jones on *Fractures and Joint Injuries*, and Macalpine on *Cystoscopy and Urography*; there are doubtless others, but they are not numerous. It is certain that Harkness on *Non-Gonococcal Urethritis* is worthy of a place in this select category.

Although the subject is one which aroused considerable interest during the last war, there is still very little known about it by those who are frequently treating it, and such expert guidance as is given in this monograph was urgently needed. It is, moreover, surprising what a large number and wide variety of conditions are included, and the title, whilst possibly not the most euphonious, is probably the only one sufficiently comprehensive. Even the addendum that it includes " the genital manifestations of local and systemic diseases and infestations of the urinary tract with protozoa, metazoa, and fungi " gives an inadequate idea of the subjects embraced.

It is the author's contention that under the influence of modern antibiotics gonorrhœa is a dying disease, but that its blood-borne complications are largely due to non-gonococcal causes which resist specific treatment; he finds non-gonococcal urethritis present in 70 per cent of patients with venereal disease, and forecasts a reversal of the prominence given to the two conditions in current teaching. It is of interest to note that methods which are now obsolete in the treatment of gonorrhœa are being used with success in non-gonococcal infections; in primary bacterial urethritis of venereal origin urethrovesical irrigations are still the most important weapon at our disposal; they must be properly given and the compressor urethræ must be " cheated into relaxation ". The prognosis is better than in abacterial (aseptic) urethritis, of which two clinical varieties are described —acute and subacute. The evidence that abacterial urethritis is due either to the virus of inclusion conjunctivitis or to pleuropneumonia-like (" L ") organisms is critically reviewed and embellished by beautiful illustrations. The acute type responds readily to the old-fashioned remedy of sandalwood oil; the subacute type (Waelsch urethritis) is more intractable and requires urethrovesical irrigations. There is no known drug, with the possible exception of aureomycin, which has any beneficial effect.

The subject of Reiter's disease occupies two chapters, and it is pointed out that it was first described by Benjamin Brodie in 1818. Distinction is made between the dysenteric and the venereal syndromes, which are probably caused by the same infective agent entering by a different portal. Treatment by chloromycetin is ineffective, but streptomycin holds more promise; urethrovesical irrigations and non-specific protein therapy are used with benefit.

The diagnosis in these diseases demands a high degree of bacteriological skill, and the author is fortunate in having the help of Mr. S. R. M. Bushby in this connexion. Diagnosis by clinical methods is still of prime importance, and the use of the aero-urethroscope is stressed. The whole subject of treatment is bound up with the development of antibiotics, and as new ones appear they should be made available for research in these diseases; such a policy would be amply repaid in a saving of man-hours. There is already included a treatment summary of drugs in order of choice for various organisms, to which frequent reference will be made.

Mention must be made of the excellence of the production and illustrations, and of the wealth of references; no statement is made without citation of its evidence, and the literary researches even include reference to a thesis in Russian! But it is the author's own expert opinion which permeates the text and gives it the touch of greatness; we congratulate him on producing a superlative monograph and a surgical classic.

The 1949 Year Book of Urology. Edited by OSWALD S. LOWSLEY, M.D., F.A.C.S., New York. $4\frac{3}{4} \times 7$ in. Pp. 445, with 62 illustrations. 1950. Chicago: The Year Book Publishers Inc. $5.00.

THIS book gives a full synopsis of all the major articles of urological interest throughout the year. As a work of reference it is invaluable; the cover quiz is not the least attractive feature.

Urological Surgery. By AUSTIN INGRAM DODSON, M.D., F.A.C.S., Professor of Urology, Medical College of Virginia, Richmond; etc. With contributions by 12 others. Second edition. $6\frac{3}{4} \times 9\frac{3}{4}$ in. Pp. 855, with 645 illustrations. 1950. London: Henry Kimpton. £4 15s.

THE second edition of this work is resplendent in a red cover with a broad green title band. The contents remain as attractive as the exterior. New sections have been added on several subjects and have brought about a slight increase in size of the book. To compensate for this the chapter on Nephroptosis has been very rightly reduced, although it still contains descriptions of seven different methods of nephropexy. Of the new chapters that on Renal Tuberculosis is one of the best. For uretero-sigmoidostomy the Coffey I operation is still preferred, and no mention is made of the current trend towards direct end-to-side anastomosis. A description of retropubic prostatectomy is included, but the reference to Millin's original articles is omitted, nor is his name spelled correctly.

The book remains a sound practical guide for the operating urologist.

The Breast. Edited by F. D. SANER, M.B., B.Ch. (Camb.), F.R.C.S. (Eng.), Surgeon, Royal Northern Hospital. 6 × 9 in. Pp. 316 + xii, with 193 illustrations, some in colour. 1950. Bristol: John Wright & Sons Ltd. 45s.

THIS monograph deals with the structure, function, and diseases of the breast and there are seventeen contributors to the volume. It might be thought that there are plenty of good books devoted to diseases of the breast and that there was little room for another. However, this is far from the truth, as our ideas as to the treatment of mammary conditions have advanced tremendously during the last decade.

The structure of the breast is well set out by Lilian Dickson and Evelyn Hewer, but the description of the lymphatic drainage of the breast is not in agreement with

the views of most surgeons who have had a large experience in the dissemination of malignant disease of the breast.

The illustrations throughout the book are of a high order and the photomicrographs could not be bettered.

Lane-Roberts and others give a good account of the function of the breast, while Broster and Raymond Greene deal with abnormalities of structure and function.

Naturally the diagnosis and treatment of mammary tumours forms the greater part of the book and Mr. Saner, who edits the volume, takes a great share in this section. Patrick Clarkson contributes a useful chapter on the value of plastic surgery in treating mammary hypertrophy and other conditions.

The book gives an up-to-date description of diseases of the breast, together with the modern trends in treatment.

It is well got up and beautifully illustrated. It should prove of real value to the undergraduate and practitioner.

An Atlas of Amputations. By DONALD B. SLOCUM, M.D., M.S. $8\frac{1}{2} \times 11$ in. Pp. 562, with 564 illustrations. 1949. London: Henry Kimpton. £7.

THIS is a very large volume on the specialized subject of amputations. The book is divided into four parts, and the material is well presented. The experience of this American surgeon is based essentially on World War II.

Part 1 deals with the indications for amputations at great length, but in a volume so large one would have expected more detailed and specific indications as to the optimum sites for amputations in relation to vascular disease and diabetes.

Part 2 deals with the surgical considerations relating to each layer in an amputation. This conforms closely to the methods employed in Britain. This section of the book also deals with anæsthesia and devotes a great deal of space to infiltration anæsthesia. A few lines are devoted to refrigeration anæsthesia, a method which is now popular, especially in America, and deserves more than passing mention.

Painful sequelæ of amputations are dealt with, but there is no clear-cut guide as to treatment and how this problem should be dealt with.

Part 3 considers surgical technique. Open amputations are dealt with at length in this section. To-day such extensive use of this procedure would not be acceptable in this country even in war-time.

Very little mention is made of the assistance obtainable from antibiotics like penicillin and streptomycin and the sulpha drugs.

Closed amputations are dealt with very thoroughly and the section on amputation of the finger deserves special mention. It is one of the best parts of the book and the author has excelled here.

The latest surgical procedures which concern the problem of arm amputations are included and the illustrations here are excellent. The Krukenberg procedure and cineplastic surgery are not very popular in the United States.

Obsolete amputations are described purely because they recur in the literature. These operations are redundant and are not even asked as surgical exercises.

Part 4 deals with the convalescent period and the complications of the final amputation.

This is a good section and the methods of handling a stump are well described. The methods used in America are very similar to those employed in this country.

The author has taken a great deal of trouble in describing the mechanics of normal gait with a prosthesis. This is not always easy to follow, but for those who are interested, this work is well presented, as is the section on prostheses.

Limb fitting in America has gone ahead rapidly, and the author thinks that with the development of plastics these will play a prominent part in the future.

There is a section on physical medicine in the treatment of the lower extremity amputations, and it is noteworthy that the Physiotherapists are in charge of this problem in the United States. This is commendable.

The book has many references, is extremely well illustrated, the paper is good, and the type clear. It should have a useful place in all medical libraries.

Surgery of the Ambulatory Patient. By L. KRAEER FERGUSON, A.B., M.D., F.A.C.S., Professor of Surgery, Graduate School of the University of Pennsylvania; etc. With a Section on Fractures by LOUIS KAPLAN, B.A., M.D., F.A.C.S., Associate in Surgery, University of Pennsylvania. Second edition. 9×6 in. Pp. 932 + xxiii, with 645 illustrations. 1948. London: J. B. Lippincott Co. 72s. net.

IN the preface to the first edition (1942) the authors considered that there was need for a text-book on the surgery which can with safety be done "in an office or out-patient clinic". He claimed that "no subject was included in the volume which cannot be cared for in an ambulatory patient".

The claim is substantiated in this the second edition, but the inclusion of new material necessitated deletions. This new material is a full discussion of chemotherapy in surgical lesions with penicillin and sulpha drugs.

New and revised sections are also devoted to tendon suture, back injuries, varicose veins, etc.

This edition, as was the first, is divided into three parts, viz., a general discussion of surgical treatment both pre- and post-operative, including anæsthesia; then the diagnosis and treatment, which may be operative, of such surgical lesions as can be dealt with in an ambulatory patient; and, finally, the section on dislocation and fractures by Louis Kaplan.

The publisher claims that the quick reference method adopted enables the practitioner to have "a split-second finding of information at his disposal".

It is now agreed that the more ambulatory a patient can be kept after any surgical procedure, the better it is for him.

It does, however, often add to the anxiety of the surgeon and may give rise to complications which otherwise would not have occurred. The principles of the safe and rapid healing of any wound, viz., rest, prevention of infection, and non-interference with blood-supply, still hold good in spite of the "penicillin umbrella" or any other chemotherapy.

The method and ideas advocated in this book would well repay study when the new health centres are being planned. At the present time they cannot be adopted by general practitioners with overcrowded surgeries and inadequate accommodation for carrying out surgical procedures.

There is no doubt, however, that a great many more surgical procedures could be done on out-patients now that hospitals are being better staffed with fully trained surgeons. There are not always sufficient beds available to keep all of them fully occupied during the sessions for which they have a contract, and the younger surgeon could be well employed teaching and training the recently qualified in the out-patient departments and thus impressing on them the importance of surgical principles, and also the fact that there is no such thing as minor surgery.

A minor procedure can very easily become a major responsibility. Proper recovery and rest rooms should be provided in every hospital out-patient department or health centre.

The book begins with details of the necessary fittings for a well-equipped office surgery. Then the various

methods of local anæsthesia are considered, instruments, etc.; this section is followed by details of wound dressings and the more common types of injury and their results, such as open wounds, infections, burns, etc. An article on the diagnosis and treatment of cutaneous and subcutaneous simple swellings closes the first part.

The second part is arranged on a 'regional surgery' basis. Many will disagree that a number of the lesions described and illustrated are suitable for ambulatory treatment. It is quite one thing for surgeons as eminent as the authors with all the necessary conveniences and staff at their disposal to deal with them, and quite another for a busy rural practitioner to attempt them when he may not be able to even procure the help of a trained nurse, let alone have time to follow up the case properly if the patient finds he is not so ambulatory after as he was before the surgical procedure, and needs skilled nursing at any rate for a few days.

With the present shortage of beds it might be quite impossible to get such a patient into hospital and the practitioner may well wish he had never attempted the operation and the result determine him never to do it again. This is certainly the case with some of the lower limb injuries described in the third part.

The book will certainly be very useful to resident house surgeons and also the trained out-patient surgeon who is attached to a hospital into which the patient can be admitted under his care, if necessary. As time goes on patients will become more and more critical of the results and become more and more inclined to allege culpable negligence if any untoward complication should occur when they have been treated as ambulatory.

The Surgical Treatment of Facial Injuries. By VARAZTAD HOVHANNES KAZANJIAN, M.D., D.M.D., Professor Emeritus of Plastic Surgery, Harvard University; etc.; and JOHN MARQUIS CONVERSE, M.D., Assistant Professor of Clinical Surgery (Plastic Surgery), New York University College of Medicine; etc. $6\frac{5}{8} \times 10$ in. Pp. 574 + xiv, with 746 illustrations. 1950. Baltimore: The Williams & Wilkins Co. (London: Baillière, Tindall & Cox.) 76s. 6d.

THE authors have attempted to cover a very large subject in a volume of readable length. To do so they have deliberately restricted themselves to descriptions of the methods of treatment they practice, with the consequence that the book is essentially practical. This positive quality will appeal to students of plastic surgery towards the beginning of their training and they will learn much from it at this stage. Ophthalmic, dental, and otorhinolaryngological surgeons will also find the chapters pertaining to their respective specialities useful for the same reason.

The more advanced student whose business it is to learn to weigh the pros and cons of different procedures in difficult situations may not find these discussed in sufficient detail.

The trained plastic surgeon will appreciate the orthodoxy of the methods advocated. If critical at all, he may feel that the snags and pitfalls could have received greater emphasis and some of the operative procedures more detailed description. The tyro will undoubtedly run into difficulties of which he has had no warning. The chapter dealing with the treatment of facial burns seemed to the reviewer particularly to deserve this criticism.

The text reads easily and the illustrations are plentiful and clear. The introductory section includes a most interesting and informative chapter on the evolution and anatomy of the face, in addition to the standard chapters on the healing and suture of wounds. A kindly understanding of the psychological problems which confront the victims of facial injuries will please all those who have had experience in trying to help these patients.

The authors have achieved their declared object, which is to teach the reader the methods of treatment which they find successful, and they are to be congratulated on restricting themselves to this despite the limitations it necessarily imposes on the book.

Essentials of Urology. By J. C. AINSWORTH-DAVIS, M.A., M.D., B.Ch. (Cantab.), F.R.C.S. (Eng., and Edin.), Urological Surgeon, The Bolingbroke Hospital, London; etc. $5\frac{5}{8} \times 8\frac{3}{4}$ in. Pp. 734 + xii, with 512 illustrations. 1950. Oxford: Blackwell Scientific Publications. 50s.

IN giving this account of urology the author lays stress on the importance of the methods of examination, both general and special, which are needed in order that a correct diagnosis may be reached. This section, which occupies about one-sixth of the volume, is probably the best. Opinions change quickly in a branch of surgery which is developing rapidly, and many will not agree with some of the procedures advocated. The tying of a gum-elastic catheter in the urethra for a week or ten days, for example, is often followed by serious urethritis, whilst a rubber or latex catheter would be better tolerated. The ambulatory treatment of papilloma by repeated short sessions of diathermy under local anæsthesia is generally now regarded as inferior in its results to one or more thorough sessions under general anæsthesia.

The description of Hunner's ulcer is somewhat remote from the accepted facts; the trigone, on which it is here depicted, is the one part of the bladder never affected, and the "ulcer" is not deeply excavated and cleanly cut.

Nevertheless, there is much useful information presented attractively, and we offer a warm welcome to a book on this subject by an English author.

Essential Urology. By FLETCHER H. COLBY, M.D., Chief of the Urological Service, Massachusetts General Hospital; etc. 6×9 in. Pp. 580 + x, with 342 illustrations. 1950. Baltimore: The Williams & Wilkins Co. (London: Baillière, Tindall & Cox.) 61s. 6d.

IF this book has been written mainly for students, as is stated in the preface, the American student must be expected to know much more about the subject than his British counterpart. There is a wealth of information on the embryology, anatomy, and physiology of the genito-urinary tract, a short section on the methods of examination, and a longer part on diseases discussed on a regional basis. Treatment is indicated on broad lines, with no detailed description of operations.

The accounts are complete and accurate without being either too verbose or too concise; at the end of each section is a list of references, mainly to the American literature, which will encourage further study of the subject. Illustrations are numerous and cover nearly every aspect of the text. We can recommend this book to every practising urologist; the undergraduate student will find in it more than he needs.

The Hinge Graft or Ginglymus Implant. By ARNOLD K. HENRY, M.B. (Dubl.), M.Ch.(Hon.) Cairo, F.R.C.S.I., Emeritus Professor of Clinical Surgery in the University of Egypt; Professor of Anatomy in the Royal College of Surgeons, Ireland. $6\frac{5}{8} \times 9\frac{5}{8}$ in. Pp. 64 + viii, with 47 illustrations. 1950. Edinburgh: E. & S. Livingstone Ltd. 15s.

PROFESSOR A. K. Henry's *Extensile Exposure Applied to Limb Surgery* was a masterpiece; his monograph on

hinge grafting unfortunately is not. He first used hinged bone-grafts for restricting movement of joints in more or less paralysed limbs (without bothering too much about restoration of muscle balance), and later had a measure of success in controlling genu recurvatum by implanting such grafts on either side of the knee. In these latter cases the gradual absorption of the grafts suggested that the beneficial effect was due to the deposition of fibrous tissue at the sites of operation. After describing these procedures his discourse turns to the use of hinged grafts for improving the usefulness of forearm stumps, and the book ends with some interesting speculations on the construction of stump extensions which are not only under voluntary control but boast some sort of cutaneous sensibility.

The critical reader will have no difficulty in picking large holes in this superbly produced and chattily written monograph, since the writer's ideas are almost wholly lacking in scientific foundation. For example, Professor Henry asks us seriously to believe that the physical properties of a piece of bone are and remain similar to those of a strip of cardboard. Yet these dilettante excursions in surgical craftsmanship might perhaps lead ultimately to some solid surgical achievement, and the book will undoubtedly interest those with experience in the reconstructive surgery of limbs. But it is not one for the bright young Registrar.

Aids to Surgical Anatomy. By J. S. BAXTER, M.D., M.Sc., F.R.C.S.I., Reader in Anatomy, University of Bristol. Third edition. $3\frac{7}{8} \times 6\frac{1}{4}$ in. Pp. 203 + viii, with 30 illustrations. 1950. London: Baillière, Tindall & Cox. 5s.

IN its revision this little book has increased somewhat in thickness, chiefly owing to the coarser paper on which it is now printed, but an addition on the autonomic nervous system is a new feature. In the section on the lymphatic drainage of the breast, the significance of involvement of the supraclavicular glands might have been mentioned with advantage and indicated on the new diagram, *Fig.* 11, which appears on page 64. Most surgeons to-day believe the connexion is via the internal mammary lymphatics and not through the apex of the axilla. The characteristic claw-hand of ulnar paralysis is more apparent after a lesion at the wrist than one at the elbow ('ulnar paradox') and the statement on page 74 is therefore rather misleading. Gray Turner, p. 125, should be Grey Turner. The terminology used is for the most part the Birmingham revision (B.R.), but Hesselbach's triangle remains: What a pity Hunter's name has gone from the adductor or subsartorial canal, and has 'lacrimal' come to stay? Some new line drawings have appeared and the revision now brings this number of the *Aids* series more in line with current practice.

BOOK NOTICES

[*The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest to readers.*]

Marknagelung nach Küntscher bei Schaftbrüchen der langen Röhrenknochen. By Prof. Dr. CARL HÄBLER, Hanover. Second edition. $6\frac{1}{8} \times 8\frac{7}{8}$. Pp. 302 + xvi, with 350 illustrations. 1950. Munich and Berlin: Urban & Schwarzenberg. DM. 26.

Les Infiltrations du Sympathique. Physiologie, Indications, Techniques. By MAURICE LUZUY. With a Foreword by Prof. R. LERICHE. Second edition. $6\frac{1}{4} \times 9\frac{3}{4}$ in. Pp. 304 + xx, with 77 illustrations. 1950. Paris: Masson et Cie. 1200 fr.

Short Textbook of Surgery. By C. F. W. ILLINGWORTH, C.B.E., M.D., Ch.M., F.R.C.S. (Edin.), Regius Professor of Surgery, University of Glasgow. Fifth edition. $6 \times 9\frac{1}{4}$ in. Pp. 676 + viii, with 233 text illustrations and 13 plates. 1950. London: J. & A. Churchill Ltd. 30s.

Supervoltage Roentgentherapy. By FRANZ BUSCHKE, M.D., SIMEON T. CANTRIL, M.D., and HERBERT M. PARKER, M.Sc., from the Tumor Institute of the Swedish Hospital, Seattle, Washington. $6 \times 9\frac{1}{4}$ in. Pp. 297 + xvi, with 260 illustrations. 1950. Springfield: Charles C. Thomas. (London: Blackwell Scientific Publications Ltd.) 77s. 6d.

Atlas typischer Röntgenbilder vom normalen Menschen. By Dr. med. RUDOLF GRASHEY. $7\frac{1}{2} \times 9\frac{3}{4}$ in. Pp. 318 + xii, with 485 text illustrations and 230 plates. 1950. Berlin: Urban & Schwarzenberg. DM. 38.

Techniques in British Surgery. Edited by RODNEY MAINGOT, F.R.C.S. $6\frac{3}{8} \times 9\frac{3}{4}$ in Pp. 733 + xx, with 473 illustrations. 1950. Philadelphia and London: W. B. Saunders Co. 75s.

Atlas of Human Anatomy, Descriptive and Regional. By M. W. WOERDEMAN, M.D., F.R.N.A.Sc., Professor of Anatomy and Embryology and Director of Anatomy Department, University of Amsterdam. Volume II, **Splanchnology, Angeiology, Nervous System, Organs of Sense**. 1950. Amsterdam: Wetenschappelijke Uitgeverij N.V. (London: Butterworth & Co. (Publishers) Ltd.) 63s.

Pre-frontal Leucotomy. A Survey of 300 Cases personally followed over 1½–3 years. By MAURICE PARTRIDGE, M.A., D.M. (Oxon.), D.P.M. (Eng.), Assistant Psychiatrist to St. George's Hospital, London. $5\frac{1}{2} \times 8\frac{1}{2}$ in. Pp. 496. 1950. Oxford: Blackwell Scientific Publications. 42s.

Lehrbuch der Röntgendiagnostik. By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL, E. UEHLINGER, with the assistance of several authors. $7\frac{3}{4} \times 11$ in. Fifth edition. Part 2. The Skeleton. Pp. 452 + vi, with 764 illustrations, some coloured. 1950. Stuttgart: Georg Thieme. DM. 70.

Plastic and Reconstructive Surgery. A Manual of Management. By FERRIS SMITH, M.D., F.A.C.S., Consultant in Plastic Surgery, Blodgett Memorial Hospital, Grand Rapids, Michigan. $6 \times 9\frac{1}{8}$ in. Pp. 895 + xxii, with 592 illustrations. 1950. Philadelphia and London: W. B. Saunders Co. 75s.

Facial Paralysis. Being a Treatise on a Clinical Classification of Paralysis of the Facial Nerve. By J. PARKES FINDLAY, M.B., Ch.M., Honorary Assistant Aural Surgeon, Sydney Hospital. $6 \times 9\frac{5}{8}$ in. Pp. 48. Illustrated. 1950. Published by Author. (Distributed by Angus & Robertson Ltd.). 17s. 6d.

The Cancer Patient. A New Chemotherapy in Advanced Cases. By B. A. MEYER, M.B., Ch.B., L.R.C.S. & P. (Edin. & Glasg.) and I. S. ORGEL, M.D. (Dublin). $4\frac{3}{4} \times 7\frac{1}{8}$ in. Pp. 87 + viii. 1950. London: J. & A. Churchill Ltd. 7s. 6d.

Os et Tuberculose. By ROBERT KAUFMANN. With a Preface by RENÉ LERICHE. $8\frac{7}{8} \times 6\frac{7}{8}$ in. Pp. 152. 1950. Paris: L'Expansion scientifique française.

Cranioplasty. By DAVID L. REEVES, A.B., M.D., Santa Barbara, California. *American Lecture Series No.* 39. $5\frac{1}{2} \times 8\frac{1}{2}$ in. Pp. 119 + x, with 71 illustrations. 1950. Springfield, Ill.: Charles C. Thomas. (Oxford: Blackwell Scientific Publications Ltd.) 22s. 6d.

Injuries to the Ankle. By J. GRANT BONNIN, M.B., B.S. (Melbourne), F.R.C.S. (Eng.), Orthopædic Surgeon, Central Middlesex Hospital. $5\frac{1}{2} \times 8\frac{3}{4}$ in. Pp. 412 + xvi, with 399 illustrations. 1950. London: William Heinemann (Medical Books) Ltd. 63s.

British Surgical Practice. General Editors: Sir ERNEST ROCK CARLING, F.R.C.S., F.R.C.P., Consulting Surgeon, Westminster Hospital; and Sir JAMES PATERSON ROSS, K.C.V.O., M.S., F.R.C.S., Surgeon and Director of Surgical Clinical Unit, St. Bartholomew's Hospital; Professor of Surgery, University of London. In eight volumes. $6\frac{3}{8} \times 8\frac{3}{8}$ in. Volume VIII. Pp. 630 + xxii, with 264 illustrations and 9 coloured plates. 1950. London: Butterworth & Co. Price per volume £3, Index £1.

The Principles of Pathology. By R. A. WILLIS, D.Sc., M.D., F.R.C.P., Professor of Pathology in the University of Leeds. $6\frac{3}{4} \times 9\frac{3}{4}$ in. Pp. 722 + xii, with 288 illustrations. 1950. London: Butterworth & Co. (Publishers) Ltd. 50s.

World Surgery, 1950. By STEPHEN A. ZIEMAN, M.A., M.D., F.A.C.S., F.I.C.S., Abstract and News Editor, Journal of the International College of Surgeons. $8\frac{1}{2} \times 11$ in. Pp. 177 + xii, with 52 illustrations. 1950. Philadelphia and London: J. B. Lippincott Co. 50s.